

What is claimed is:

1. A method for treating or preventing a  
5 neoplasia disorder in a mammal in need of such treatment  
or prevention, which method comprises administering to  
said mammal a therapeutically-effective amount of a  
combination of a cyclooxygenase-2 inhibitor, an integrin  
10 antagonist, and an antineoplastic agent, wherein said  
antineoplastic agent is selected from the group  
consisting of anastrozole, calcium carbonate,  
capecitabine, carboplatin, cisplatin, Cell Pathways CP-  
461, docetaxel, doxorubicin, etoposide, fluorouracil (5-  
FU), fluoxymestrine, gemcitabine, goserelin, irinotecan,  
15 ketoconazole, letrozol, leucovorin, levamisole,  
megestrol, mitoxantrone, paclitaxel, raloxifene,  
retinoic acid, tamoxifen, thiotepa, topotecan,  
toremifene, vinorelbine, vinblastine, vincristine,  
selenium (selenomethionine), ursodeoxycholic acid,  
20 sulindac sulfone, exemestane and eflornithine (DFMO).

2. The method of Claim 1 wherein the combination  
is administered in a sequential manner.

25 3. The method of Claim 1 wherein the combination  
is administered in a substantially simultaneous manner.

4. The method of Claim 1 wherein the  
antineoplastic agent is capecitabine.

5. The method of Claim 1 wherein the antineoplastic agent is carboplatin.

6. The method of Claim 1 wherein the  
5 antineoplastic agent is cisplatin.

7. The method of Claim 1 wherein the antineoplastic agent is Cell Pathways CP-461.

10 8. The method of Claim 1 wherein the antineoplastic agent is docetaxel.

9. The method of Claim 1 wherein the antineoplastic agent is doxorubicin.  
15

10. The method of Claim 1 wherein the antineoplastic agent is etoposide.

11. The method of Claim 1 wherein the  
20 antineoplastic agent is fluoxymestrine.

12. The method of Claim 1 wherein the antineoplastic agent is gemcitabine.

25 13. The method of Claim 1 wherein the antineoplastic agent is goserelin.

14. The method of Claim 1 wherein the antineoplastic agent is irinotecan.  
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15. The method of Claim 1 wherein the antineoplastic agent is ketoconazole.

16. The method of Claim 1 wherein the  
5 antineoplastic agent is letrozol.

17. The method of Claim 1 wherein the antineoplastic agent is leucovorin.

10 18. The method of Claim 1 wherein the antineoplastic agent is levamisole.

19. The method of Claim 1 wherein the antineoplastic agent is megestrol.

15 20. The method of Claim 1 wherein the antineoplastic agent is mitoxantrone.

20 21. The method of Claim 1 wherein the antineoplastic agent is paclitaxel.

22. The method of Claim 1 wherein the antineoplastic agent is raloxifene.

25 23. The method of Claim 1 wherein the antineoplastic agent is retinoic acid.

24. The method of Claim 1 wherein the antineoplastic agent is tamoxifen.

30

25. The method of Claim 1 wherein the antineoplastic agent is thiotepa.

26. The method of Claim 1 wherein the  
5 antineoplastic agent is topotecan.

27. The method of Claim 1 wherein the antineoplastic agent is toremifene.

10 28. The method of Claim 1 wherein the antineoplastic agent is vinorelbine.

29. The method of Claim 1 wherein the antineoplastic agent is vinblastine.

15 30. The method of Claim 1 wherein the antineoplastic agent is vincristine.

31. The method of Claim 1 wherein the  
20 antineoplastic agent is selenium (selenomethionine).

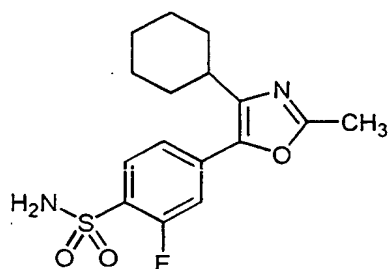
32. The method of Claim 1 wherein the antineoplastic agent is sulindac sulfone.

25 33. The method of Claim 1 wherein the antineoplastic agent is eflornithine (DFMO).

34. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is selected from compounds,  
30 and their pharmaceutically acceptable salts thereof, of the group consisting of:

-221-

1)



JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-  
2-fluorobenzenesulfonamide,

5

2)

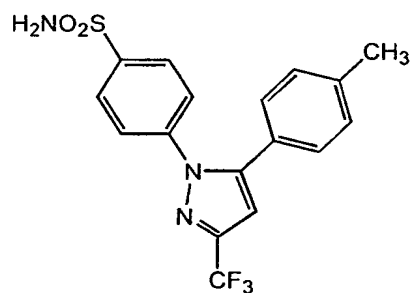
5-chloro-3-(4-(methylsulfonyl)phenyl)-2-  
(methyl-5-pyridinyl)pyridine,

3)

2-(3,5-difluorophenyl)-3-4-  
(methylsulfonyl)phenyl)-2-cyclopenten-1-one,

10

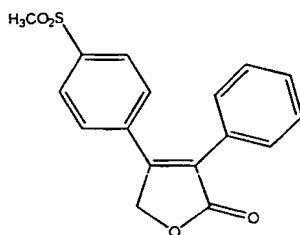
4)



4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-  
pyrazol-1-yl]-benzenesulfonamide,

-222-

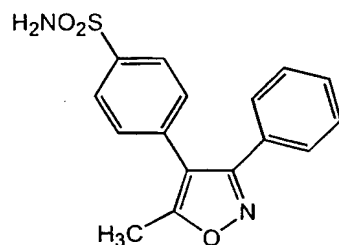
5)



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone,

5

6)

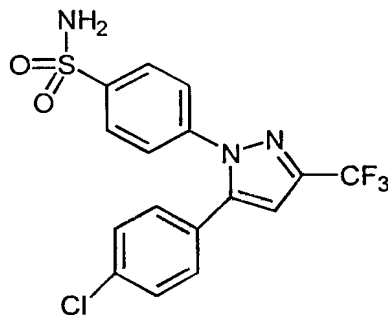


4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide,

7) N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide,

10

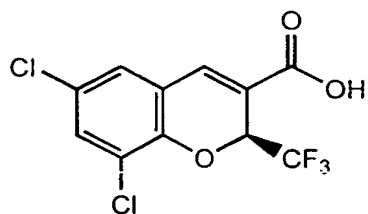
8)



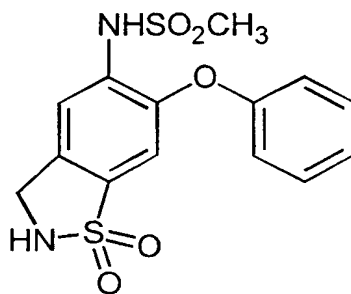
4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,

-223-

9)

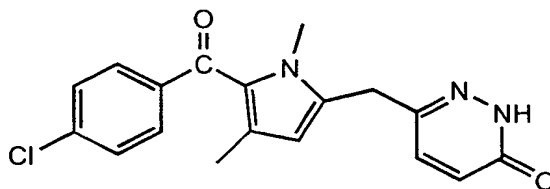


10)



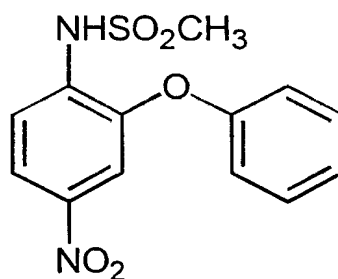
5

11)



6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

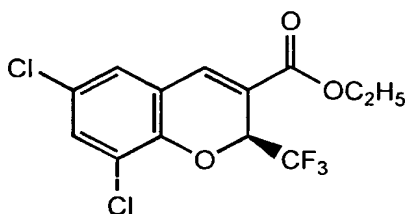
12)



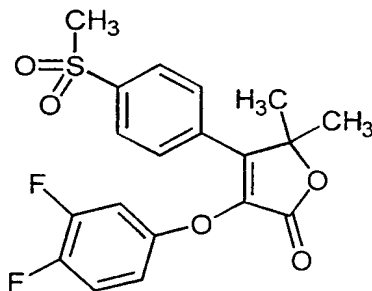
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N-(4-nitro-2-phenoxyphenyl)methanesulfonamide,

13)



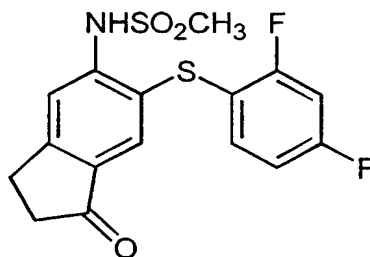
14)



5

3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,

15)



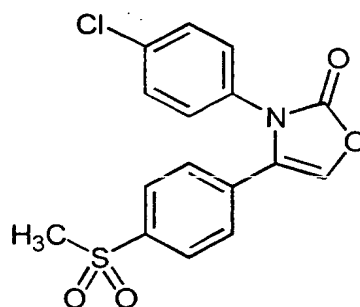
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N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,



-225-

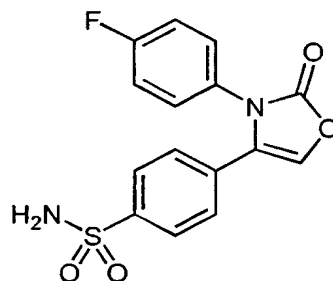
16)



3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

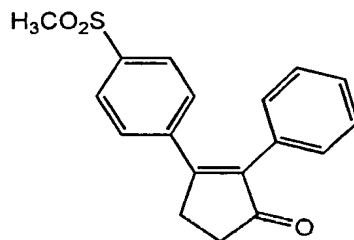
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17)



4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

18)

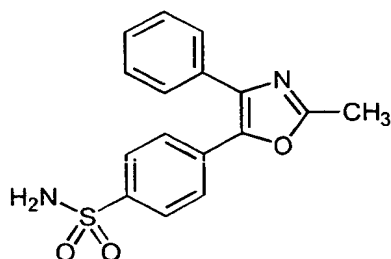


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3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,

-226-

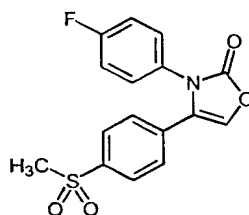
19)



4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,

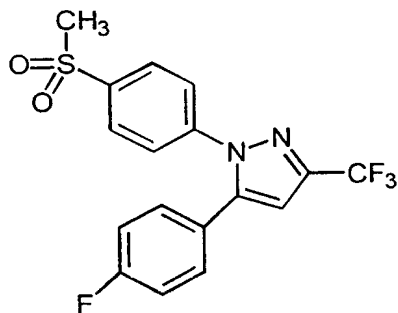
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20)



3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

21)

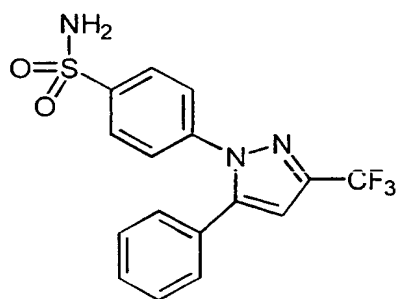


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5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,

-227-

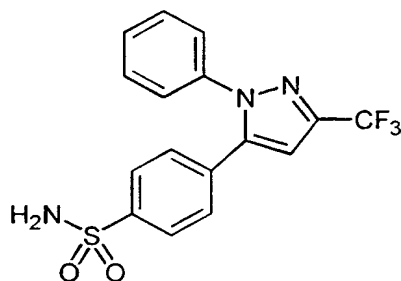
22)



4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

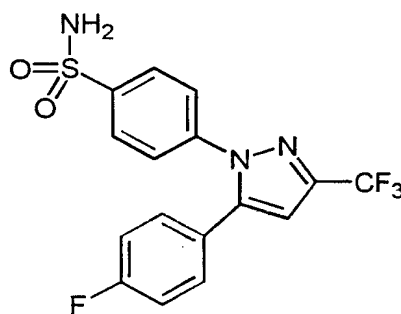
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23)



4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,

24)

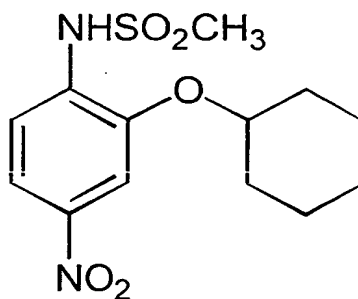


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4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

-228-

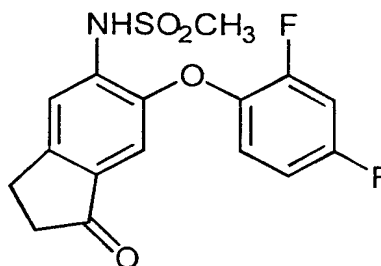
25)



N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide,

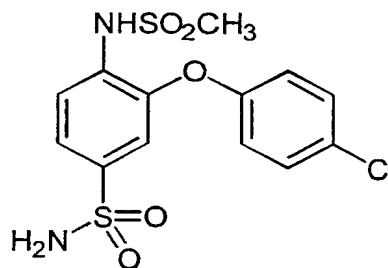
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26)



N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

27)

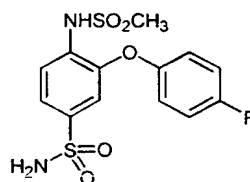


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3-(4-chlorophenoxy)-4-[(methanesulfonyl)amino]benzenesulfonamide,

-229-

28)

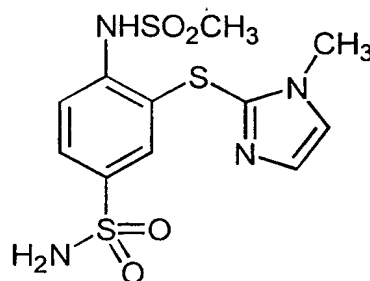


3-(4-fluorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

5

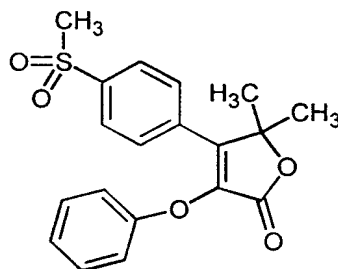
29)



3-[(1-methyl-1H-imidazol-2-yl)thio]-4

[(methylsulfonyl) amino]benzenesulfonamide,

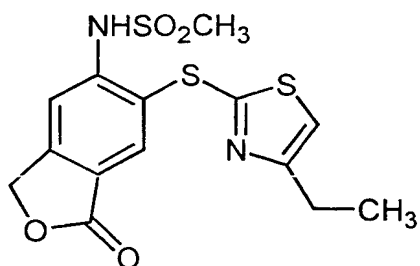
30)



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5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-  
phenoxy-2(5H)-furanone,

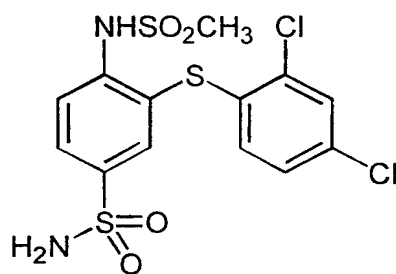
31)



N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

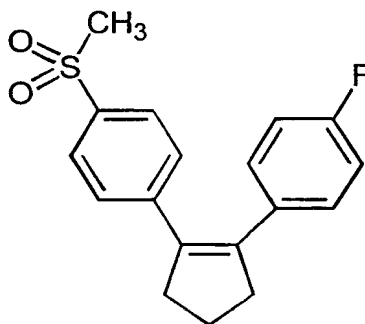
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32)



3-[(2,4-dichlorophenyl)thio]-4-[(methanesulfonyl)amino]benzenesulfonamide,

33)

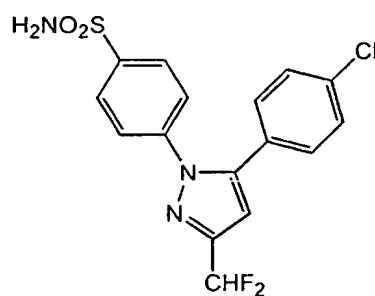


10

1-fluoro-4-[2-[4-(methanesulfonyl)phenyl]cyclopenten-1-yl]benzene,

-231-

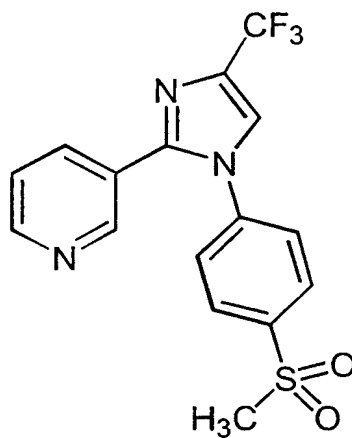
34)



4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

5

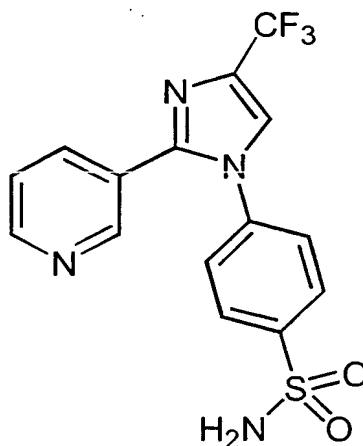
35)



3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

-232-

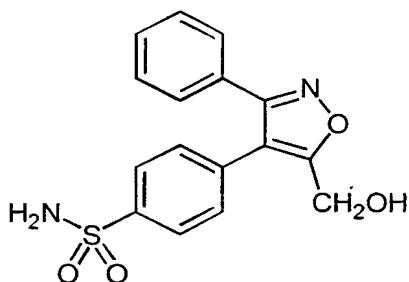
36)



4-[2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide,

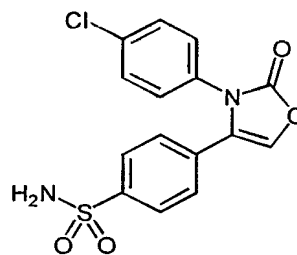
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37)



4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

38)



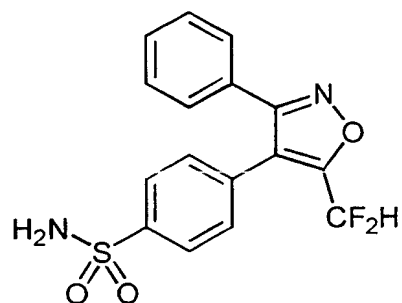
10

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,



-233-

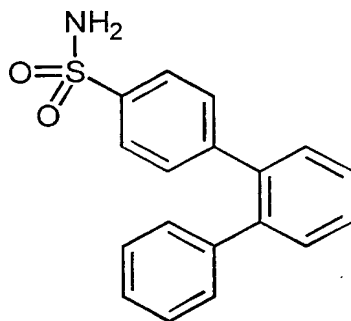
39)



4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

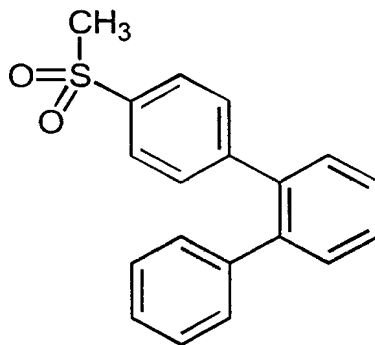
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40)



[1,1':2',1''-terphenyl]-4-sulfonamide,

41)

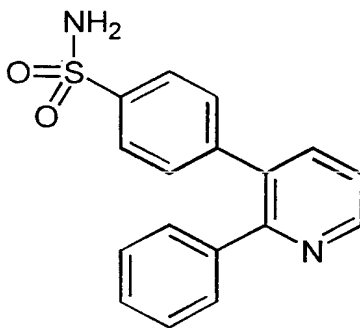


10

4-(methylsulfonyl)-1,1',2],1''-terphenyl,

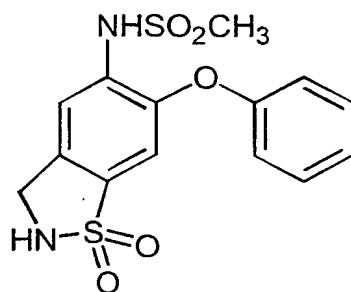
-234-

42)



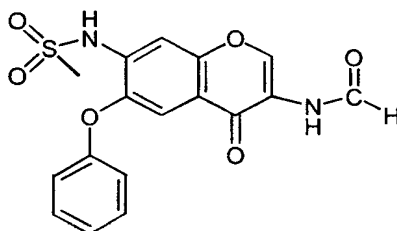
4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

43)



N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and

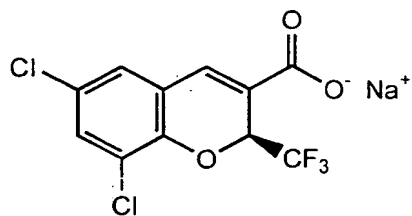
44)



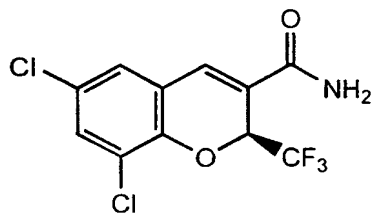
N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

-235-

45)

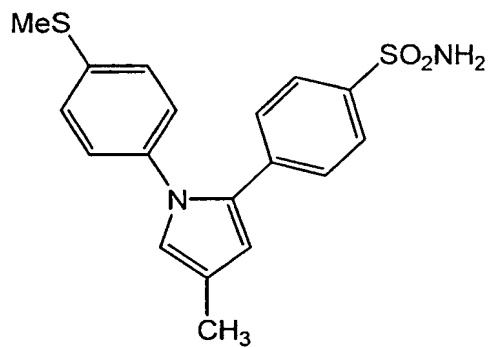


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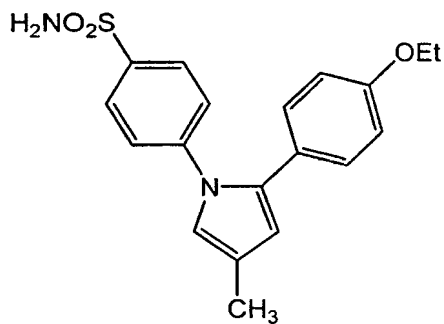
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47)



, and

48)

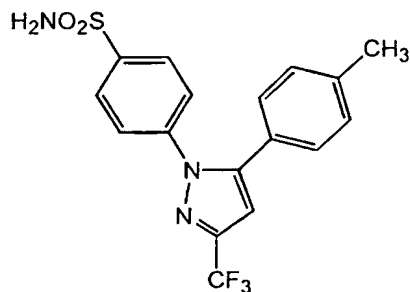


35. The method of Claim 1 wherein the  
10 cyclooxygenase-2 inhibitor is 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.

-236-

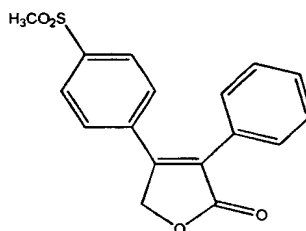
36. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.

37. The method of Claim 1 wherein the  
5 cyclooxygenase-2 inhibitor is



4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

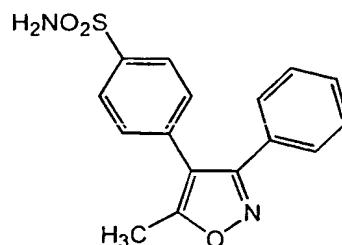
38. The method of Claim 1 wherein the  
10 cyclooxygenase-2 inhibitor is



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone.

-237-

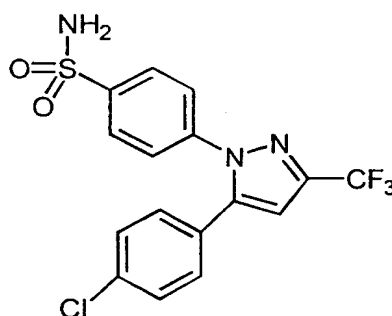
39. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is



5 4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide.

40. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is N-[[4-(5-methyl-3-phenylisoxazol-4yl)phenyl]sulfonyl]propanamide.

41. The method of Claim 1 wherein the  
10 cyclooxygenase-2 inhibitor is



4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide.

42. The method of Claim 1 wherein the neoplasia is  
15 selected from the group consisting of lung cancer, breast cancer, gastrointestinal cancer, bladder cancer, head and neck cancer and cervical cancer.

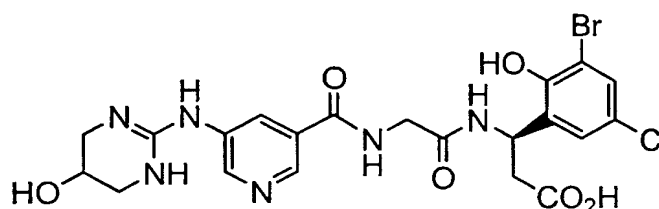
43. The method of Claim 1 wherein the neoplasia is  
20 selected from the group consisting of acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cystic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, bartholin gland carcinoma,

basal cell carcinoma, bronchial gland carcinomas,  
capillary, carcinoids, carcinoma, carcinosarcoma,  
cavernous, cholangiocarcinoma, chondrosarcoma, choroid  
plexus papilloma/carcinoma, clear cell carcinoma,  
5 cystadenoma, endodermal sinus tumor, endometrial  
hyperplasia, endometrial stromal sarcoma, endometrioid  
adenocarcinoma, ependymal, epithelioid, Ewing's sarcoma,  
fibrolamellar, focal nodular hyperplasia, gastrinoma,  
germ cell tumors, glioblastoma, glucagonoma,  
10 hemangiblastomas, hemangioendothelioma, hemangiomas,  
hepatic adenoma, hepatic adenomatosis, hepatocellular  
carcinoma, insulinoma, intraepithelial neoplasia,  
interepithelial squamous cell neoplasia, invasive  
squamous cell carcinoma, large cell carcinoma,  
15 leiomyosarcoma, lentigo maligna melanomas, malignant  
melanoma, malignant mesothelial tumors, medulloblastoma,  
medulloepithelioma, melanoma, meningeal, mesothelial,  
metastatic carcinoma, mucoepidermoid carcinoma,  
neuroblastoma, neuroepithelial adenocarcinoma nodular  
20 melanoma, oat cell carcinoma, oligodendroglial,  
osteosarcoma, pancreatic polypeptide, papillary serous  
adenocarcinoma, pineal cell, pituitary tumors,  
plasmacytoma, pseudosarcoma, pulmonary blastoma, renal  
cell carcinoma, retinoblastoma, rhabdomyosarcoma,  
25 sarcoma, serous carcinoma, small cell carcinoma, soft  
tissue carcinomas, somatostatin-secreting tumor,  
squamous carcinoma, squamous cell carcinoma,  
submesothelial, superficial spreading melanoma,  
undifferentiated carcinoma, uveal melanoma, verrucous  
30 carcinoma, vipoma, well differentiated carcinoma, and  
Wilm's tumor.

44. The method of Claim 1 wherein the integrin antagonist is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group

5 consisting of:

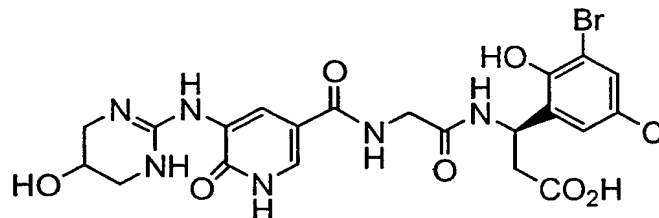
1)



(3R)-N-[[5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-

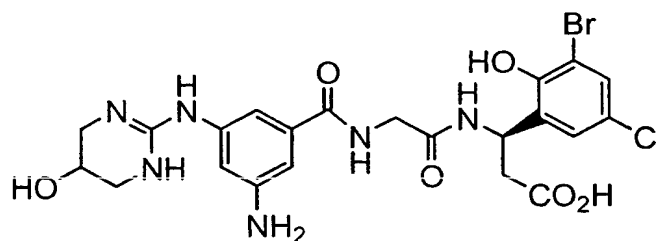
3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

2)



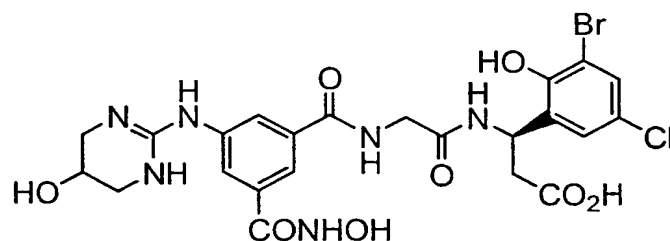
(3R)-N-[[1,6-dihydro-6-oxo-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

3)



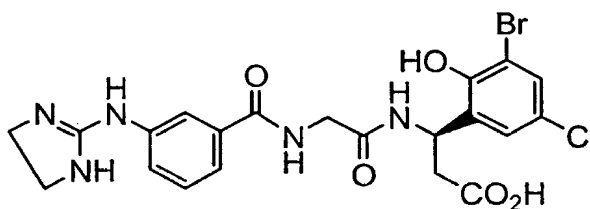
(3R)-N-[3-amino-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

4)



(3R)-N-[3-[(hydroxyamino)carbonyl]-5-[(1,4,5,6-tetrahydro-5-hydroxy)-2-pyrimidinyl]amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

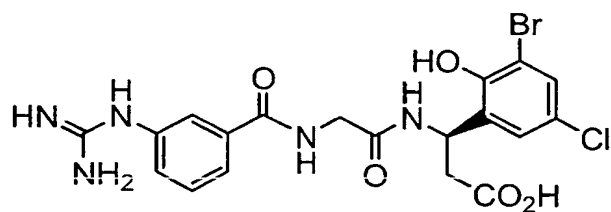
5)



(3R)-N-[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,



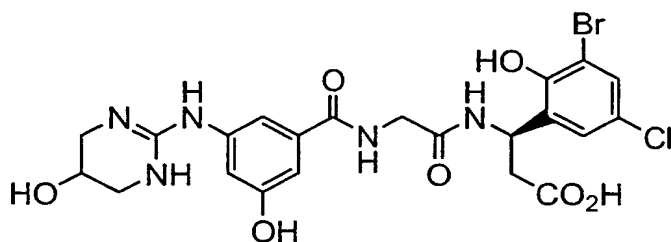
6)



(3R) -N- [3-

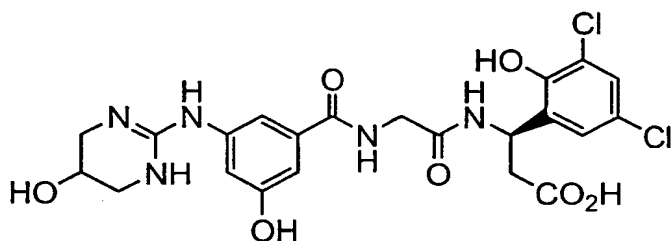
[ (aminoiminomethyl) amino] benzoyl] glycyl-3- (3-  
bromo-5-chloro-2-hydroxyphenyl) -b-alanine,

7)



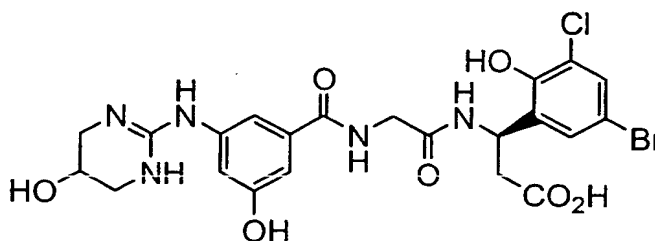
(3R) -N- [3-hydroxy-5- [ (1,4,5,6-tetrahydro-5-  
hydroxy-2-pyrimidinyl) amino] benzoyl] glycyl-3-  
(3-bromo-5-chloro-2-hydroxyphenyl) -b-alanine,

8)



(3R) -N- [3-hydroxy-5- [ (1,4,5,6-tetrahydro-5-  
hydroxy-2-pyrimidinyl) amino] benzoyl] glycyl-3-  
(3,5-dichloro-2-hydroxyphenyl) -b-alanine,

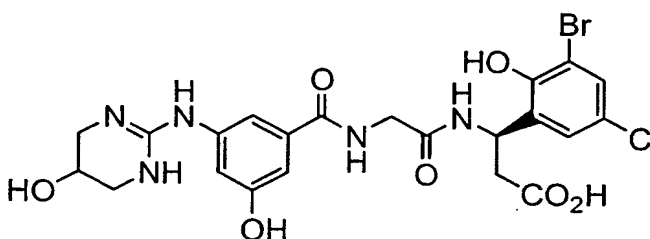
9)



(3R) -N - [3-hydroxy-5 - [ (1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl) amino]benzoyl]glycyl-3-(5-bromo-3-chloro-2-hydroxyphenyl) -b-alanine,

5

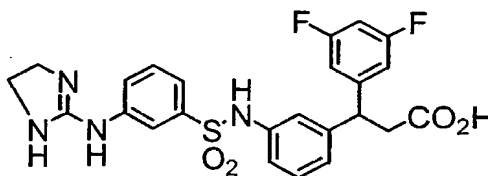
10)



(3R) -N - [3-hydroxy-5 - [ (1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl) amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl) -b-alanine,

10

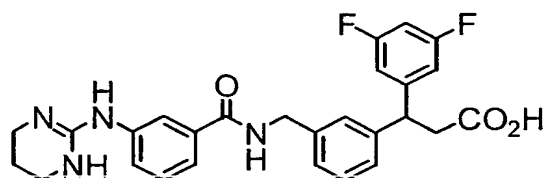
11)



b - [3 - [ [ [3 - [ [4,5-dihydro-1H-imidazol-2-yl) amino] phenyl] sulfonyl] amino] phenyl] - 3,5-difluorobenzenepropanoic acid,

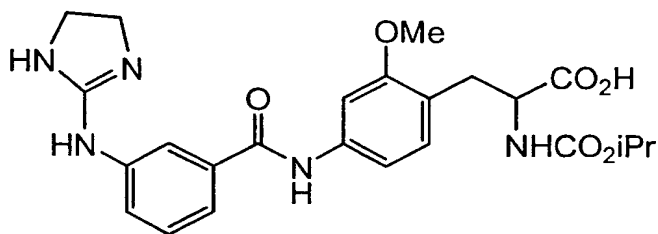
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12)

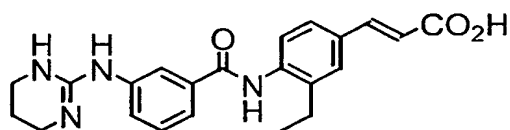


3,5-difluoro-b-[3-[[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]methyl]phenyl] benzenepropanoic acid,

13)

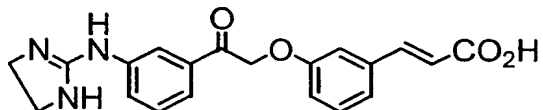


14)



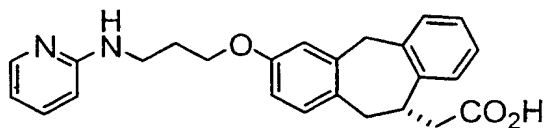
(2E)-3-[3-ethyl-4-[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]phenyl]-2-propenoic acid,

15)



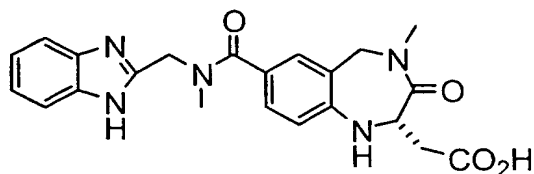
(2E)-3-[3-[2-[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]-2-oxoethoxy]phenyl]-2-propenoic acid,

16)



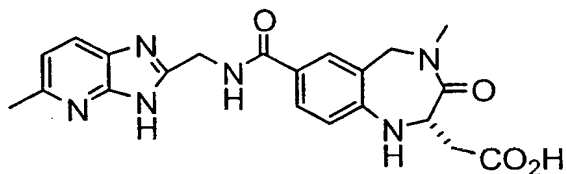
(10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid,

17)



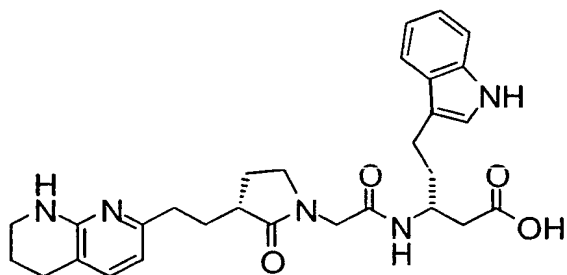
(2S)-7-[[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid,

18)



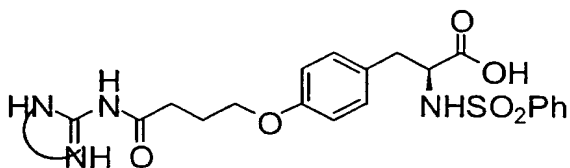
(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid,

19)

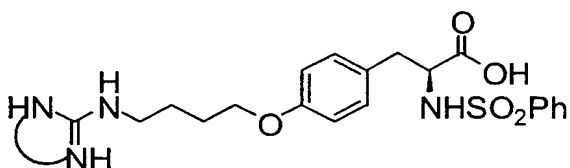


(bR) -b-[[[(3R)-2-oxo-3-[2-(1,5,6,7-tetrahydro-  
1,8-naphthyridin-2-yl)ethyl]-1-  
pyrrolidinyl]acetyl]amino]-1H-indole-3-  
pentanoic acid,

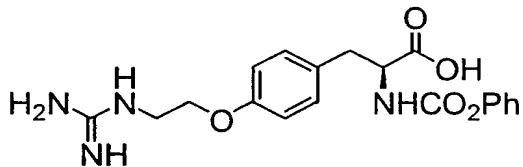
20)



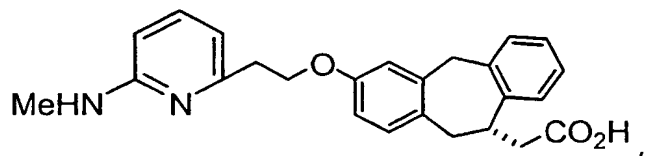
21)



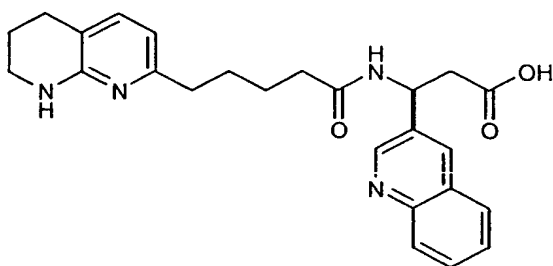
22)



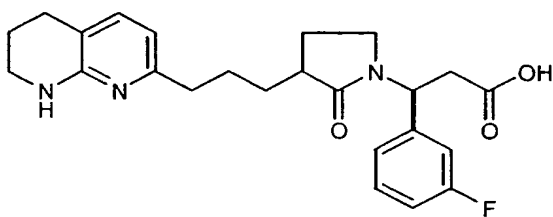
23)



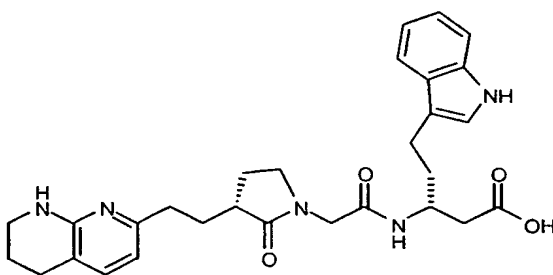




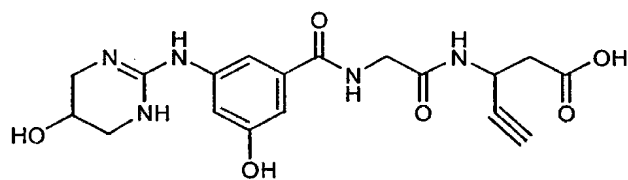
30)



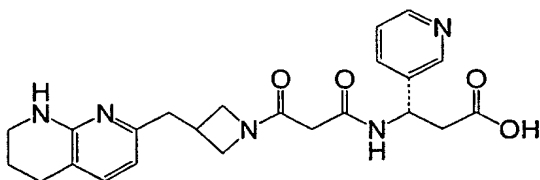
31)



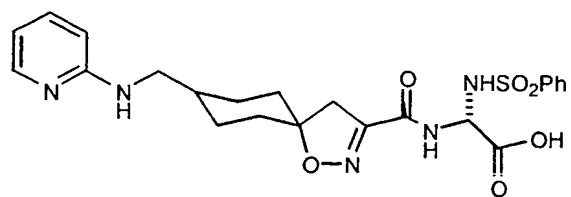
32)



33)

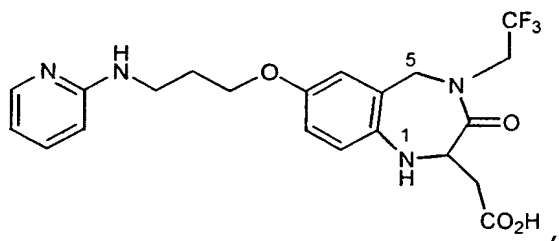


34)

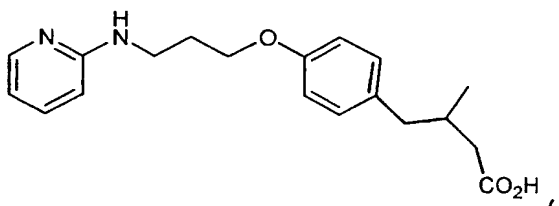


35)

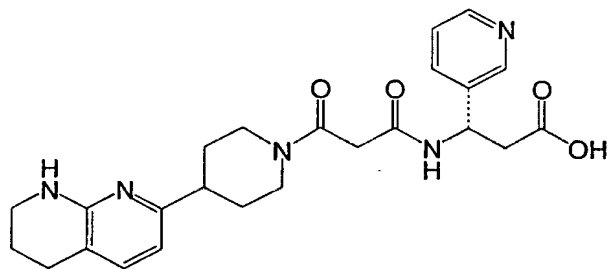
5



36)

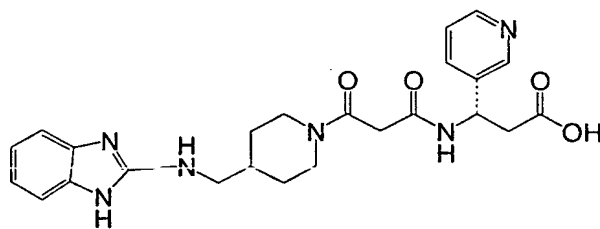


37)

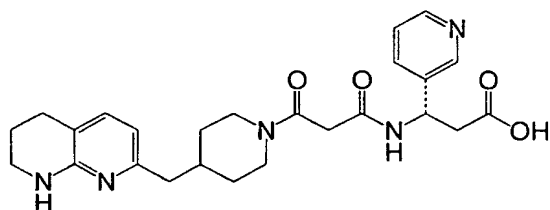




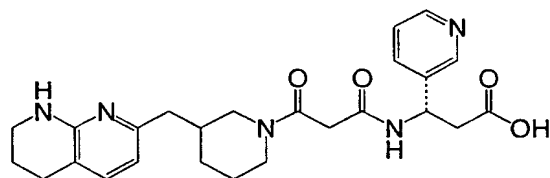
38)



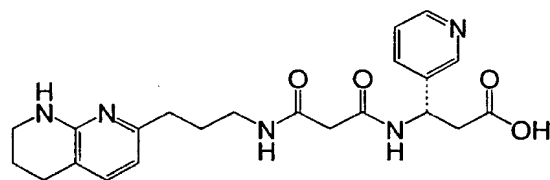
39)



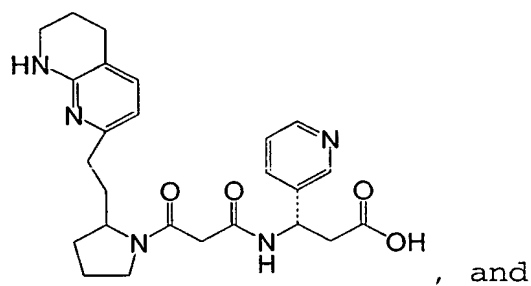
40)



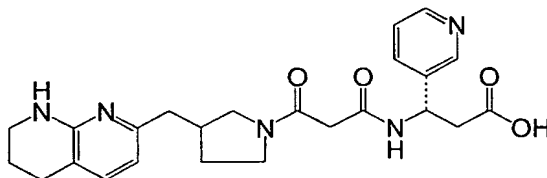
41)



42)

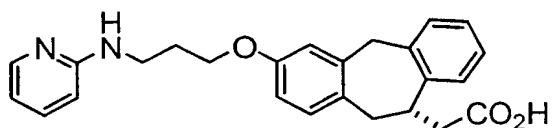


43)



5

45. The method of Claim 1 wherein the integrin antagonist is

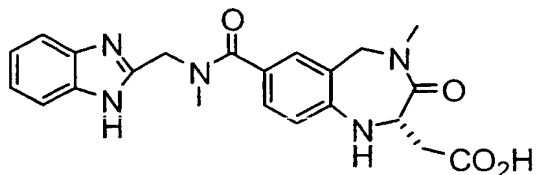


10

(10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid.

-251-

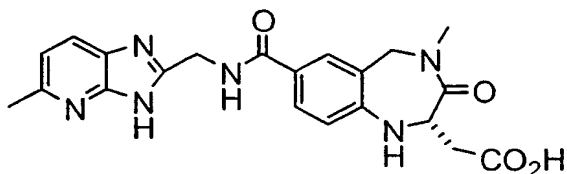
46. The method of Claim 1 wherein the integrin antagonist is



5

(2S)-7-[[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid.

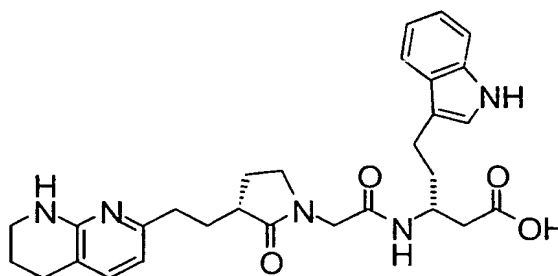
47. The method of Claim 1 wherein the integrin antagonist is



10

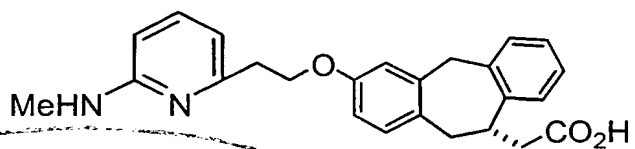
(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid.

48. The method of Claim 1 wherein the integrin antagonist is



5 (bR)-b-[[[(3R)-2-oxo-3-[2-(1,5,6,7-tetrahydro-1,8-naphthyridin-2-yl)ethyl]-1-pyrrolidinyl]acetyl]amino]-1H-indole-3-pentanoic acid.

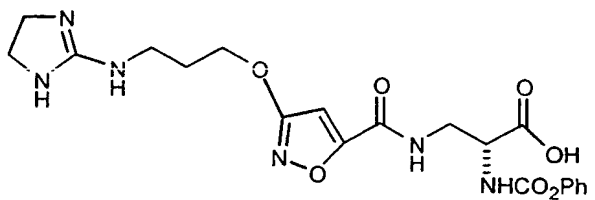
49. The method of Claim 1 wherein the integrin  
10 antagonist is



50. The method of Claim 1 wherein the integrin  
15 antagonist is Vitaxin antibody(Ixsys).

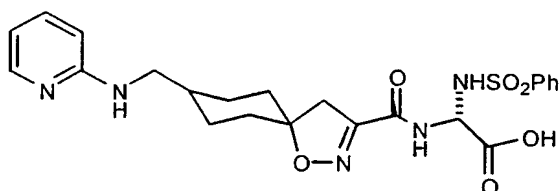
51. The method of Claim 1 wherein the integrin antagonist is Merck KGaA EMD-121974, cyclo[RGDf-N(Me)V-]

52. The method of Claim 1 wherein the integrin antagonist is



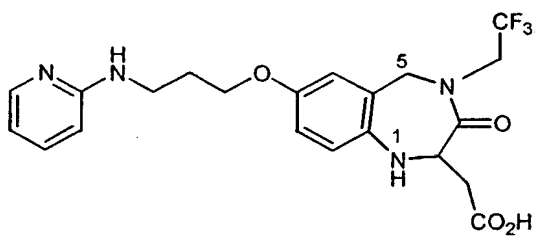
5

53. The method of Claim 1 wherein the integrin antagonist is



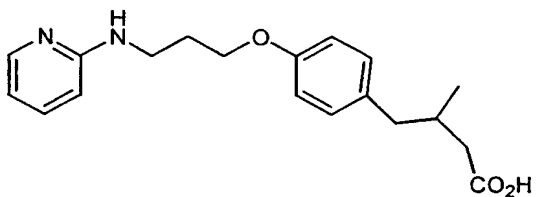
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54. The method of Claim 1 wherein the integrin antagonist is



15

55. The method of Claim 1 wherein the integrin antagonist is



56. A method for treating or preventing a neoplasia disorder in a mammal in need of such treatment or prevention, which method comprises administering to said mammal a therapeutically-effective amount of a  
5 combination of radiation, a cyclooxygenase-2 inhibitor, an integrin antagonist, and an antineoplastic agent, wherein said antineoplastic agent is selected from the group consisting of anastrozole, calcium carbonate, capecitabine, carboplatin, cisplatin, Cell Pathways CP-  
10 461, docetaxel, doxorubicin, etoposide, fluorouracil (5-FU), fluoxymestrine, gemcitabine, goserelin, irinotecan, ketoconazole, letrozol, leucovorin, levamisole, megestrol, mitoxantrone, paclitaxel, raloxifene, retinoic acid, tamoxifen, thiotepa, topotecan,  
15 toremifene, vinorelbine, vinblastine, vincristine, selenium (selenomethionine), ursodeoxycholic acid, sulindac sulfone, exemestane and eflornithine (DFMO).

57. The method of Claim 56 wherein the combination  
20 is administered in a sequential manner.

58. The method of Claim 56 wherein the combination is administered in a substantially simultaneous manner.

25 59. The method of Claim 56 wherein the antineoplastic agent is capecitabine.

60. The method of Claim 56 wherein the antineoplastic agent is carboplatin.

61. The method of Claim 56 wherein the antineoplastic agent is cisplatin.

5 62. The method of Claim 56 wherein the antineoplastic agent is Cell Pathways CP-461.

63. The method of Claim 56 wherein the antineoplastic agent is docetaxel.

10

64. The method of Claim 56 wherein the antineoplastic agent is doxorubicin.

15 65. The method of Claim 56 wherein the antineoplastic agent is etoposide.

66. The method of Claim 56 wherein the antineoplastic agent is fluoxymestrine.

20 67. The method of Claim 56 wherein the antineoplastic agent is gemcitabine.

68. The method of Claim 56 wherein the antineoplastic agent is goserelin.

25

69. The method of Claim 56 wherein the antineoplastic agent is irinotecan.

30 70. The method of Claim 56 wherein the antineoplastic agent is ketoconazole.

-256-

72. The method of Claim 56 wherein the antineoplastic agent is letrozol.

73. The method of Claim 56 wherein the  
5 antineoplastic agent is leucovorin.

74. The method of Claim 56 wherein the antineoplastic agent is levamisole.

10 75. The method of Claim 56 wherein the antineoplastic agent is megestrol.

76. The method of Claim 56 wherein the antineoplastic agent is mitoxantrone.  
15

77. The method of Claim 56 wherein the antineoplastic agent is paclitaxel.

78. The method of Claim 56 wherein the  
20 antineoplastic agent is raloxifene.

79. The method of Claim 56 wherein the antineoplastic agent is retinoic acid.

25 80. The method of Claim 56 wherein the antineoplastic agent is tamoxifen.

81. The method of Claim 56 wherein the antineoplastic agent is thiotepa.  
30



82. The method of Claim 56 wherein the antineoplastic agent is topotecan.

83. The method of Claim 56 wherein the  
5 antineoplastic agent is toremifene.

84. The method of Claim 56 wherein the antineoplastic agent is vinorelbine.

10 85. The method of Claim 56 wherein the antineoplastic agent is vinblastine.

86. The method of Claim 56 wherein the  
15 antineoplastic agent is vincristine.

87. The method of Claim 56 wherein the antineoplastic agent is selenium (selenomethionine).

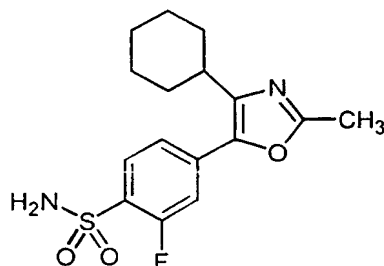
88. The method of Claim 56 wherein the  
20 antineoplastic agent is sulindac sulfone.

89. The method of Claim 56 wherein the antineoplastic agent is eflornithine (DFMO).

25 90. The method of Claim 56 wherein the cyclooxygenase-2 inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

-258-

1)



JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-  
2-fluorobenzenesulfonamide,

5

2)

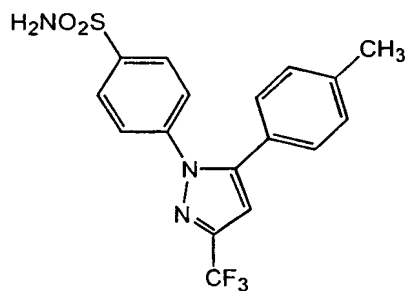
5-chloro-3-(4-(methylsulfonyl)phenyl)-2-  
(methyl-5-pyridinyl)pyridine,

3)

2-(3,5-difluorophenyl)-3-4-  
(methylsulfonyl)phenyl)-2-cyclopenten-1-one,

10

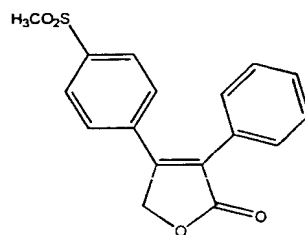
4)



4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-  
pyrazol-1-yl]-benzenesulfonamide,

-259-

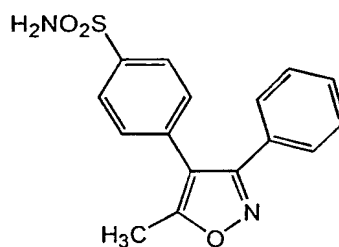
5)



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone,

5

6)



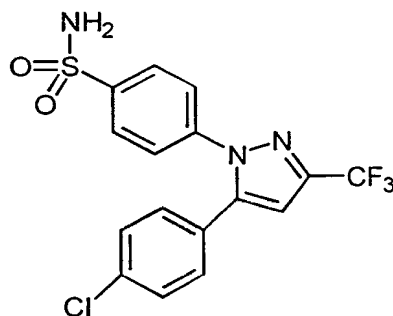
4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide,

7)

N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide,

10

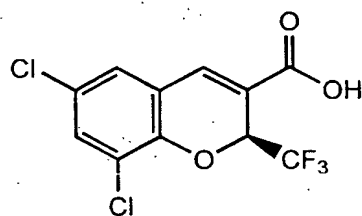
8)



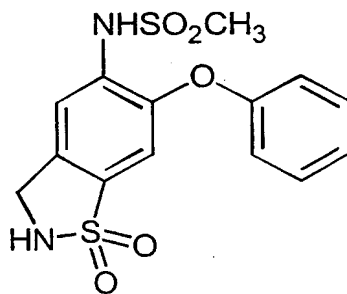
4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,

-260-

9)

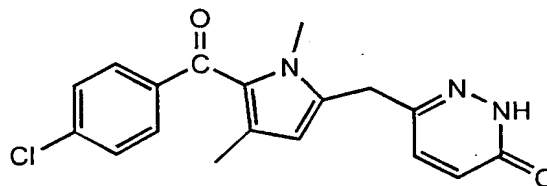


10)



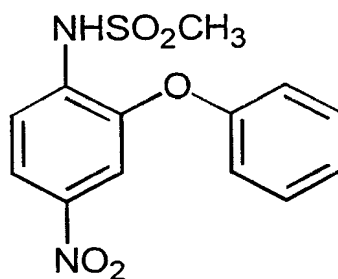
5

11)



6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

12)

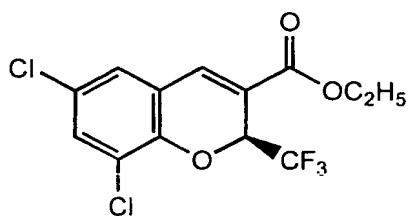


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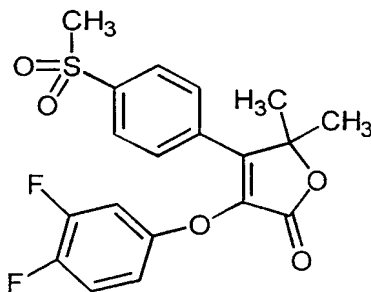
N-(4-nitro-2-phenoxyphenyl)methanesulfonamide,

-261-

13)



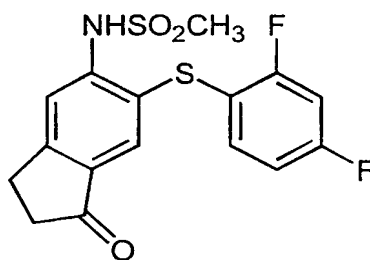
14)



5

3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,

15)

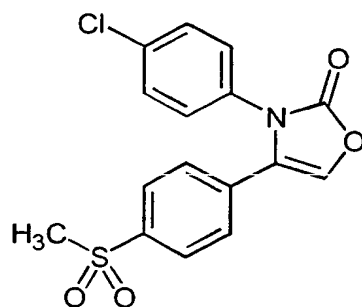


10

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

-262-

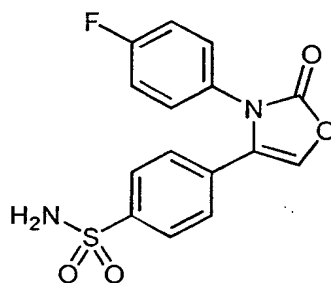
16)



3-(4-chlorophenyl)-4-[4-(  
(methylsulfonyl)phenyl]-2(3H)-oxazolone,

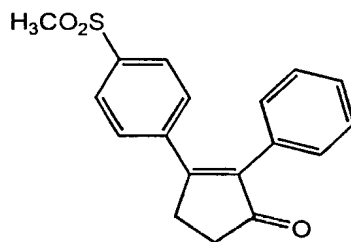
5

17)



4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-  
oxazolyl]benzenesulfonamide,

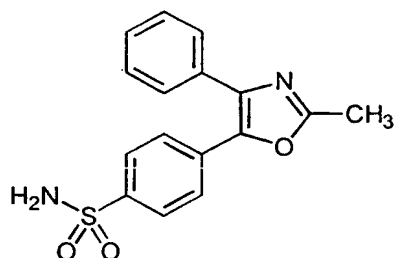
18)



10

3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-  
cyclopenten-1-one,

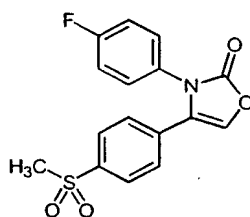
19)



4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,

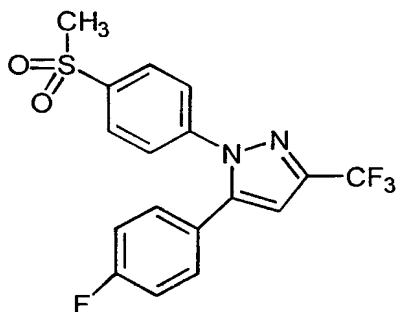
5

20)



3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

21)

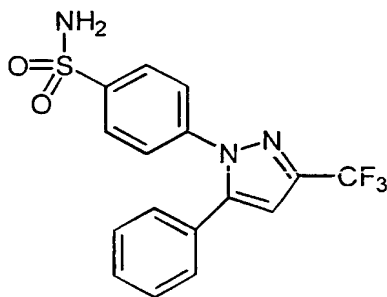


10

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,

-264-

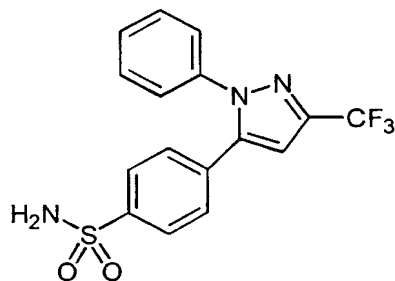
22)



4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

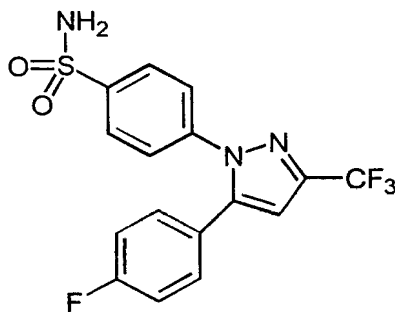
5

23)



4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,

24)



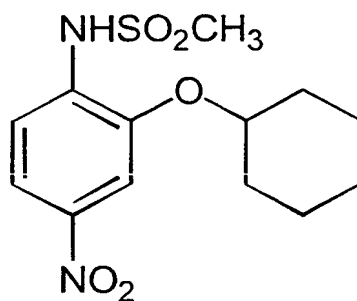
10

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,



-265-

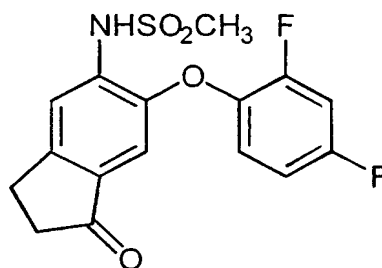
25)



N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide,

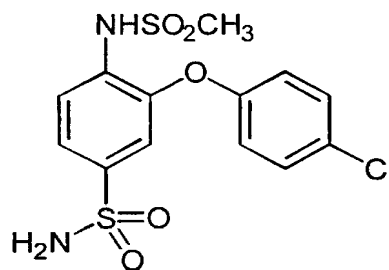
5

26)



N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

27)



10

3-(4-chlorophenoxy)-4-[(methanesulfonyl)amino]benzenesulfonamide,

-266-

28)

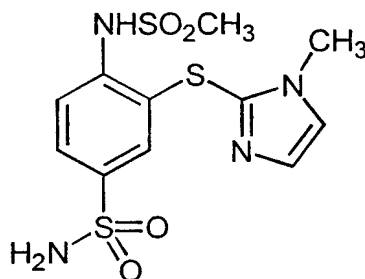


3-(4-fluorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

5

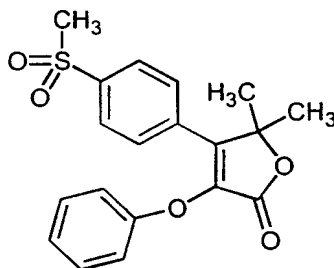
29)



3-[(1-methyl-1H-imidazol-2-yl)thio]-4

[(methylsulfonyl)amino]benzenesulfonamide,

30)

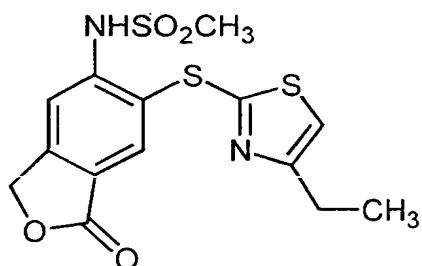


10

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-  
phenoxy-2(5H)-furanone,

-267-

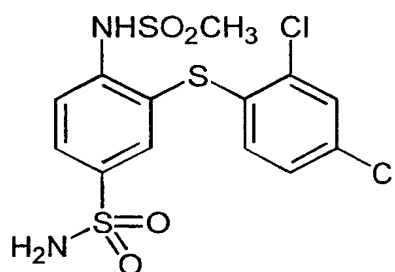
31)



N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

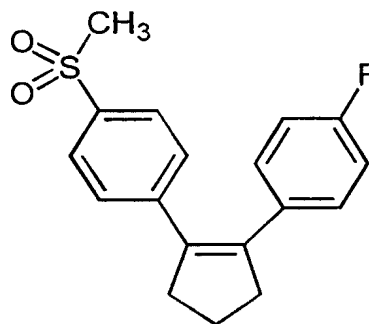
5

32)



3-[(2,4-dichlorophenyl)thio]-4-[(methanesulfonyl)amino]benzenesulfonamide,

33)

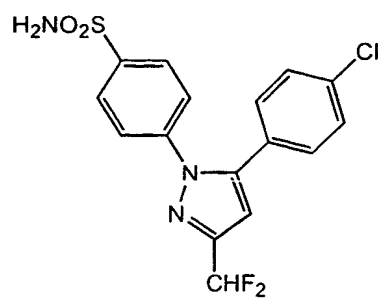


10

1-fluoro-4-[2-[4-(methanesulfonyl)phenyl]cyclopenten-1-yl]benzene,

-268-

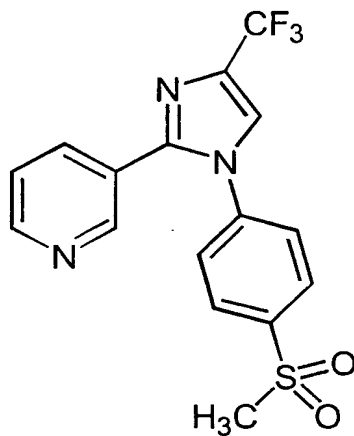
34)



4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

5

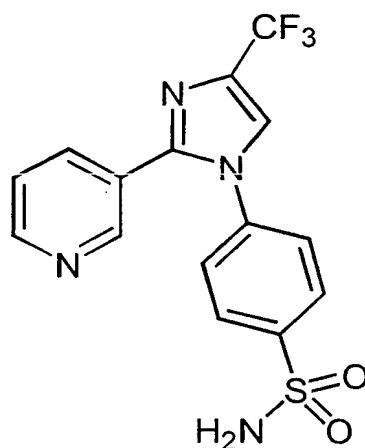
35)



3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

-269-

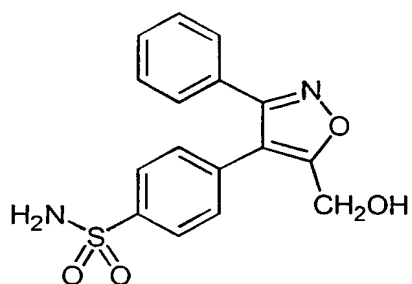
36)



4-[2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide,

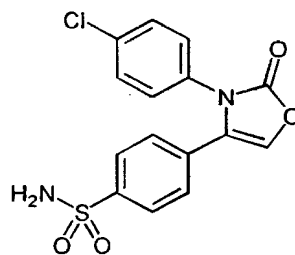
5

37)



4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

38)

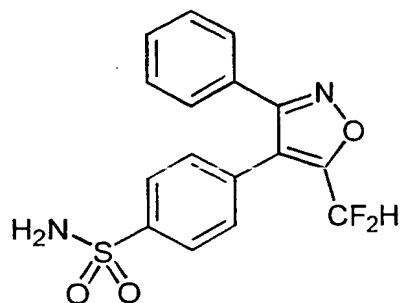


10

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

-270-

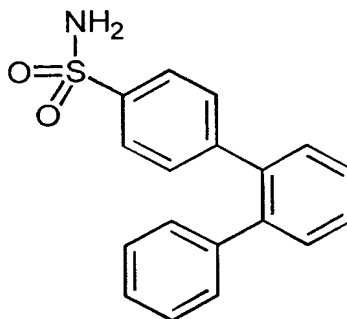
39)



4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

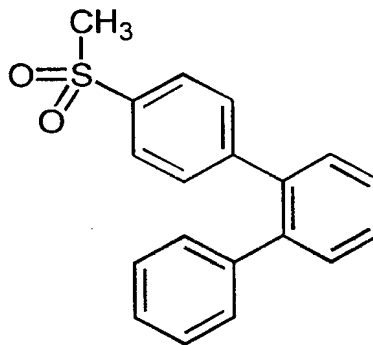
5

40)



[1,1':2',1''-terphenyl]-4-sulfonamide,

41)

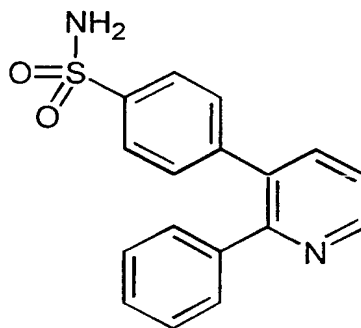


10

4-(methylsulfonyl)-1,1',2],1''-terphenyl,

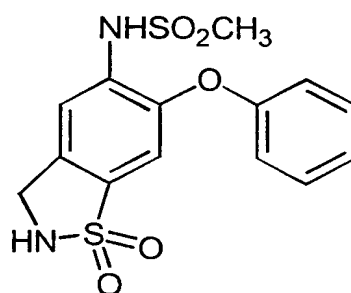
-271-

42)



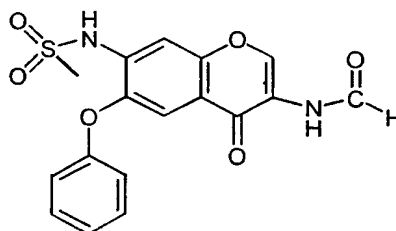
4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

43)



N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and

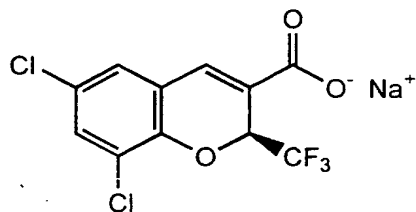
44)



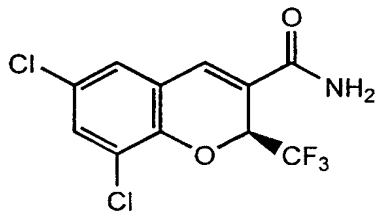
N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

-272-

45)

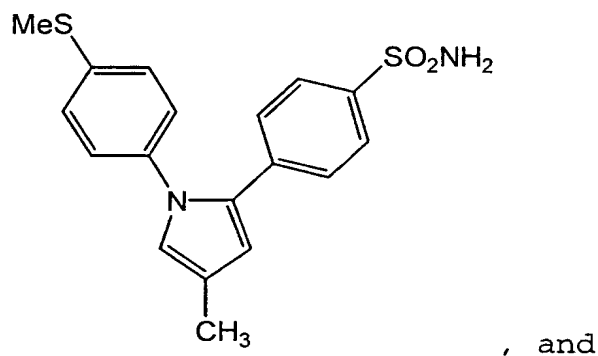


46)

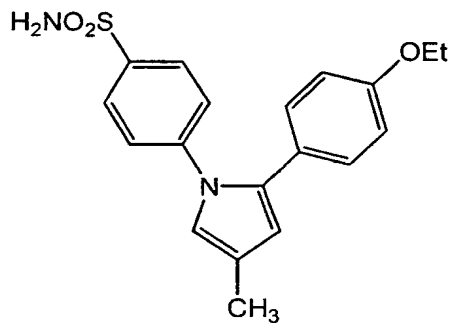


5

47)



48)



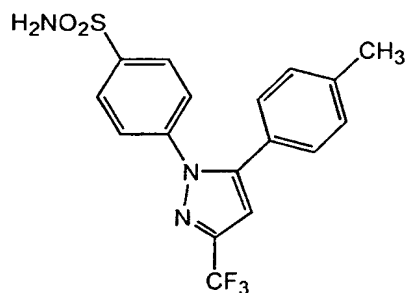
91. The method of Claim 56 wherein the  
10 cyclooxygenase-2 inhibitor is 5-chloro-3-(4-(methanesulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.



-273-

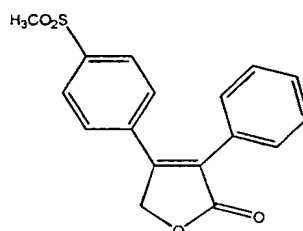
92. The method of Claim 56 wherein the cyclooxygenase-2 inhibitor is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.

93. The method of Claim 56 wherein the  
5 cyclooxygenase-2 inhibitor is



4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

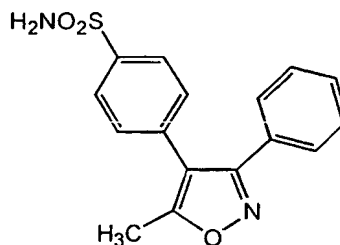
94. The method of Claim 56 wherein the  
10 cyclooxygenase-2 inhibitor is



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone.

-274-

95. The method of Claim 56 wherein the cyclooxygenase-2 inhibitor is



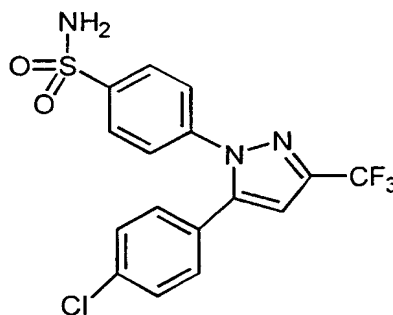
4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide.

5

96. The method of Claim 56 wherein the cyclooxygenase-2 inhibitor is N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide.

97. The method of Claim 56 wherein the cyclooxygenase-2 inhibitor is

10



4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide.

98. The method of Claim 56 wherein the neoplasia is selected from the group consisting of lung cancer, breast cancer, gastrointestinal cancer, bladder cancer, head and neck cancer and cervical cancer.

99. The method of Claim 56 wherein the neoplasia is selected from the group consisting of acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cystic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, bartholin

20

gland carcinoma, basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, cavernous, cholangiocarcinoma, chondrosarcoma, choroid plexus papilloma/carcinoma, clear

5 cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma,

10 glucagonoma, hemangioblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intraepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma,

15 leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular

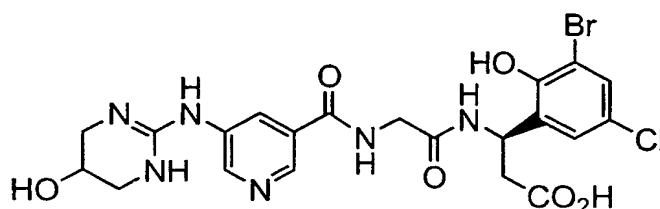
20 melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma,

25 sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous

30 carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor.

100. The method of Claim 56 wherein the integrin antagonist is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

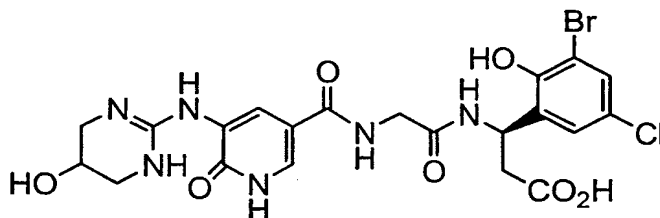
1)



(3R)-N-[[5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-

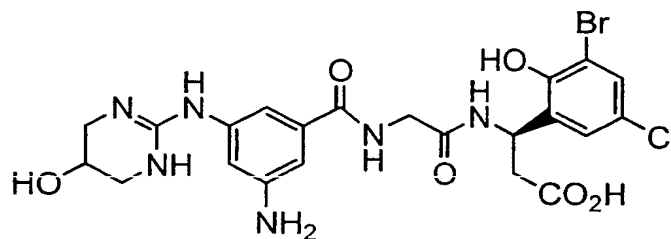
3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

2)



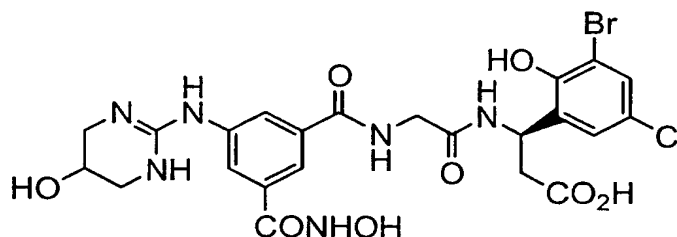
(3R)-N-[[1,6-dihydro-6-oxo-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

3)



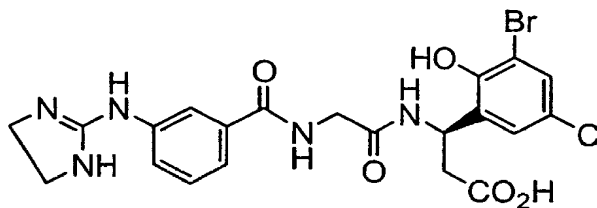
(3R)-N-[3-amino-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

4)



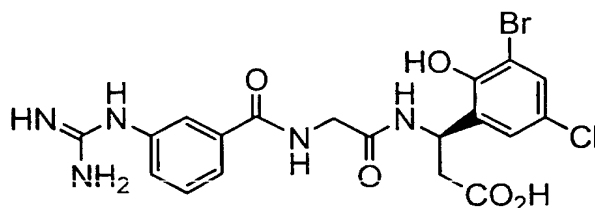
(3R)-N-[3-[(hydroxyamino)carbonyl]-5-[(1,4,5,6-tetrahydro-5-hydroxy)-2-pyrimidinyl]amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

5)



(3R)-N-[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

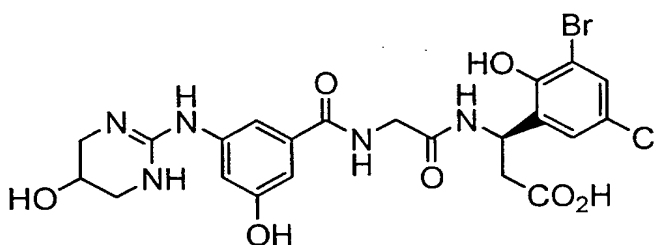
6)



(3R)-N-[3-

[(aminoiminomethyl)amino]benzoyl]glycyl-3-(3-  
bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

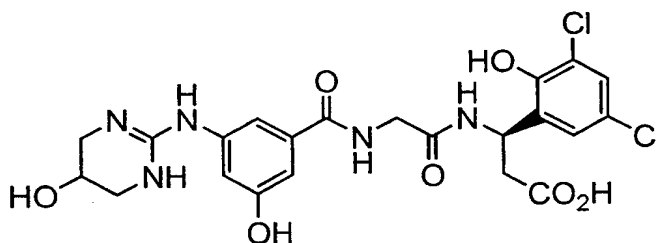
7)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-

hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-  
(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

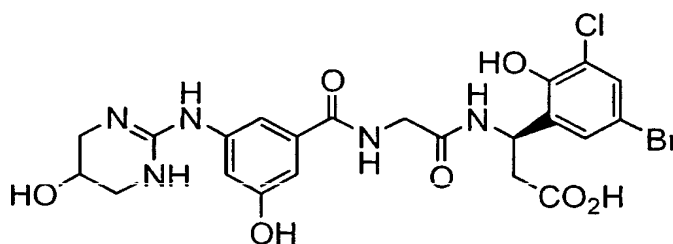
8)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-

hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-  
(3,5-dichloro-2-hydroxyphenyl)-L-alanine,

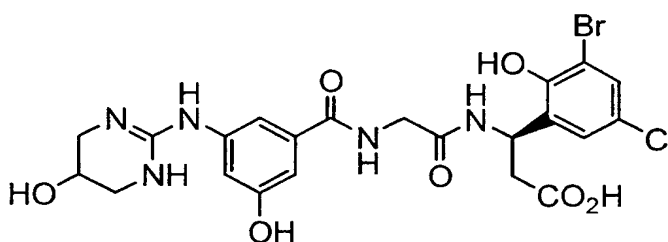
9)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(5-bromo-3-chloro-2-hydroxyphenyl)-L-alanine,

5

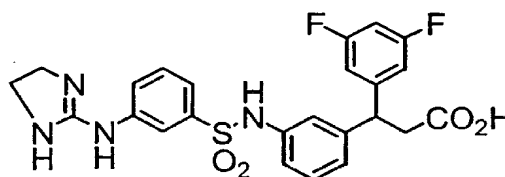
10)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

10

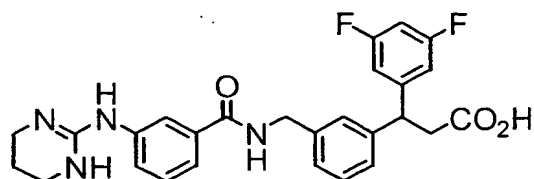
11)



L-[3-[[[3-[[4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]sulfonyl]amino]phenyl]-3,5-difluorobenzenepropanoic acid,

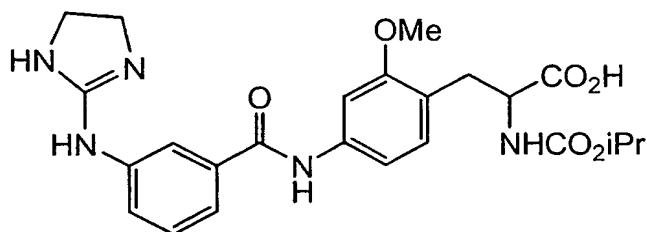
15

12)

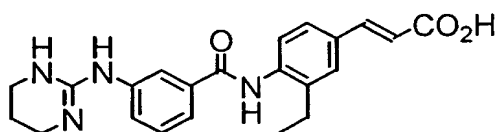


3,5-difluoro-b-[3-[[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]methyl]phenyl] benzenepropanoic acid,

13)

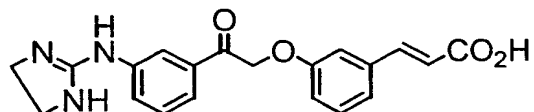


14)



(2E)-3-[3-ethyl-4-[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]phenyl]-2-propenoic acid,

15)

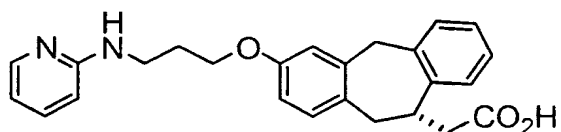


(2E)-3-[3-[2-[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]-2-oxoethoxy]phenyl]-2-propenoic acid,



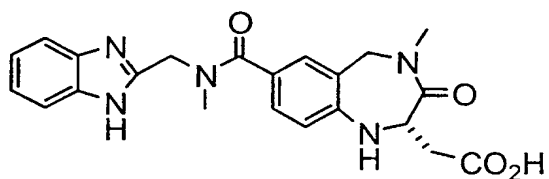
-281-

16)



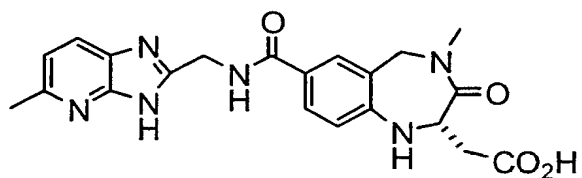
(10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid,

17)



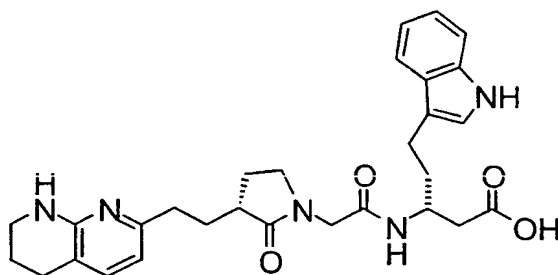
(2S)-7-[[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid,

18)



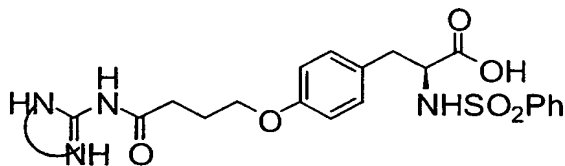
(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid,

19)



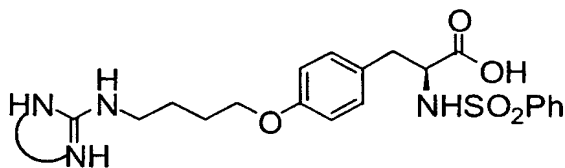
(bR) -b- [ [ (3R) -2-oxo-3-[2-(1,5,6,7-tetrahydro-  
1,8-naphthyridin-2-yl)ethyl]-1-  
pyrrolidinyl]acetyl]amino]-1H-indole-3-  
pentanoic acid,

20)

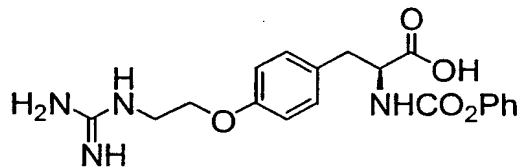


10

21)

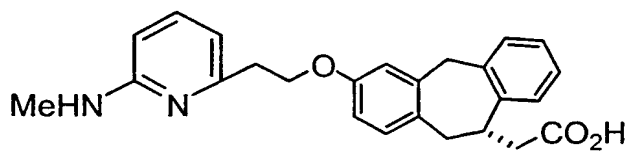


22)



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23)

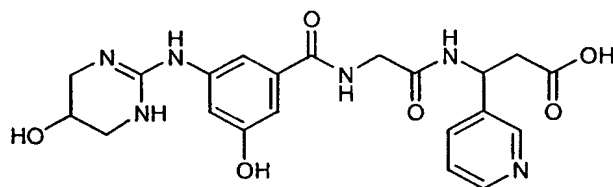


24) Vitaxin antibody(Ixsys),

25) Merck KGaA EMD-121974, cyclo[RGDf-N(Me)V-],

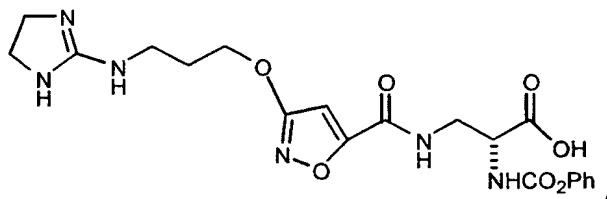
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26)

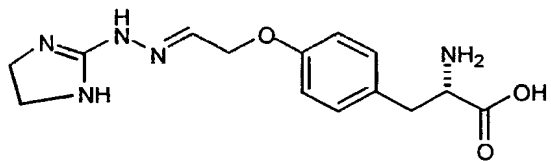


10

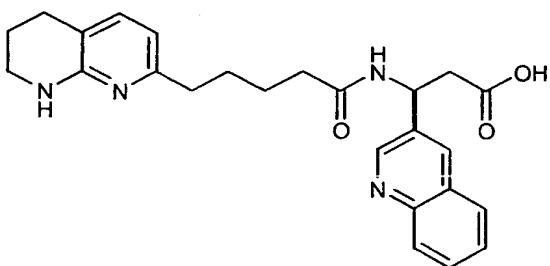
27)



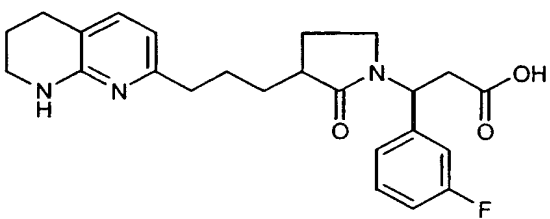
28)



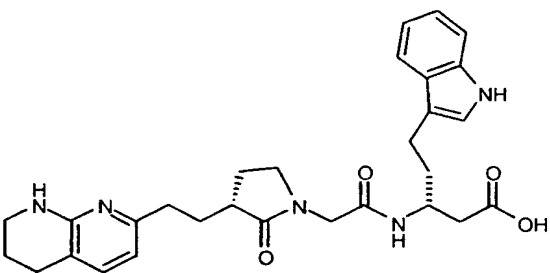
15



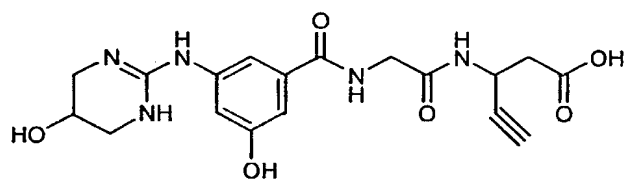
30)



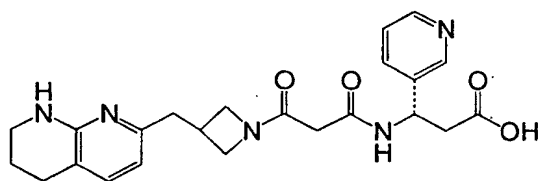
31)



32)

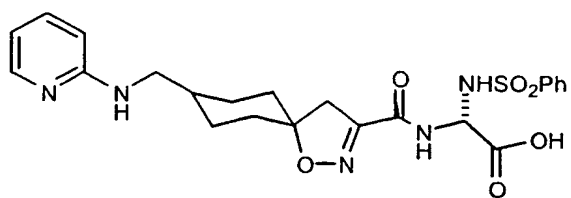


33)



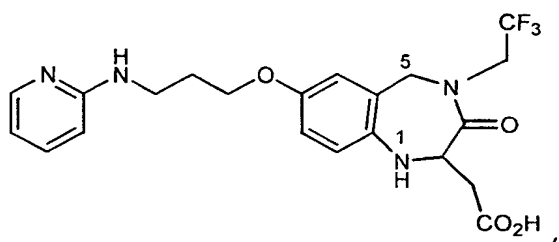
-285-

34)

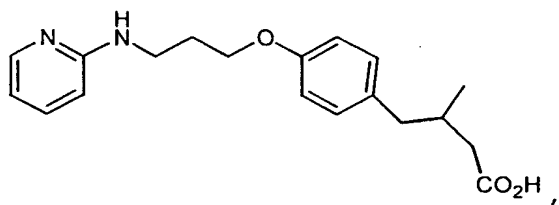


35)

5

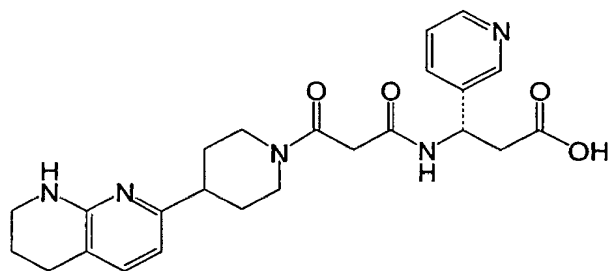


36)

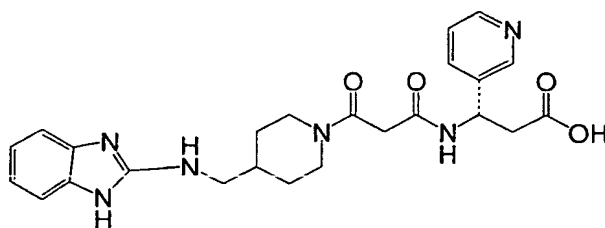


10

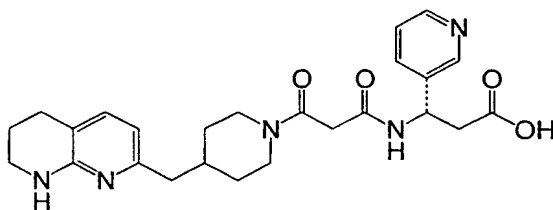
37)



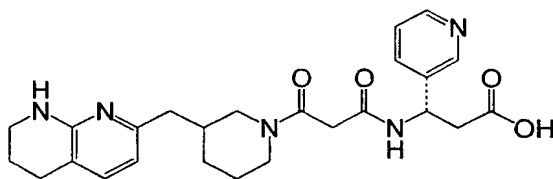
38)



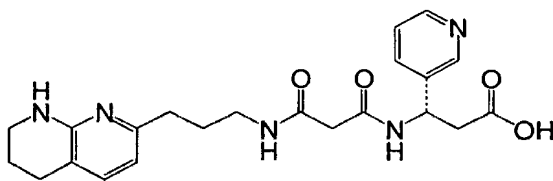
39)



40)

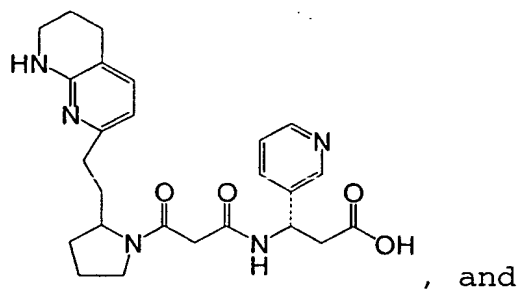


41)

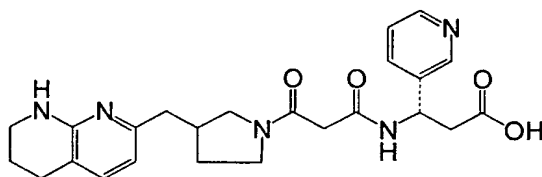


-287-

42)

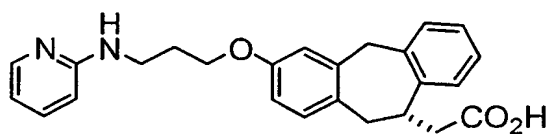


43)



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101. The method of Claim 56 wherein the integrin antagonist is

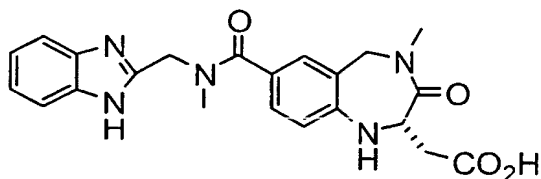


10

(10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid.

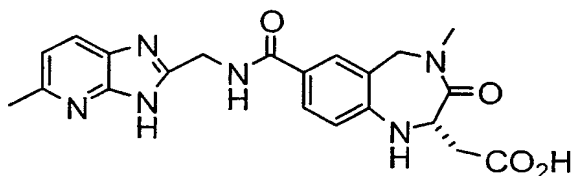
-288-

102. The method of Claim 56 wherein the integrin antagonist is



(2S)-7-[[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid.

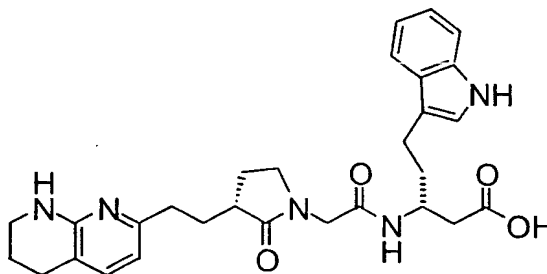
103. The method of Claim 56 wherein the integrin antagonist is



(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid.

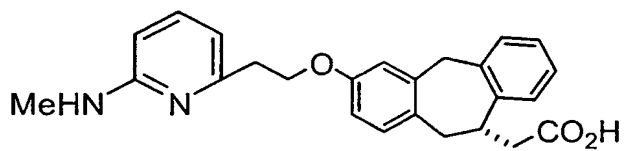


104. The method of Claim 56 wherein the integrin antagonist is



5 (bR)-b-[[[(3R)-2-oxo-3-[2-(1,5,6,7-tetrahydro-1,8-naphthyridin-2-yl)ethyl]-1-pyrrolidinyl]acetyl]amino]-1H-indole-3-pentanoic acid.

10 105. The method of Claim 56 wherein the integrin antagonist is

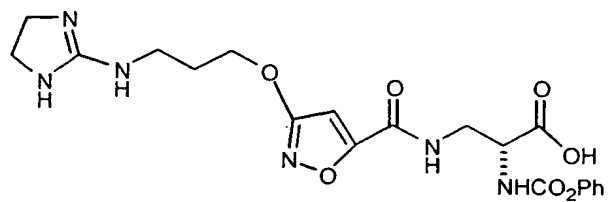


15 106. The method of Claim 56 wherein the integrin antagonist is Vitaxin antibody(Ixsys).

107. The method of Claim 56 wherein the integrin antagonist is Merck KGaA EMD-121974, cyclo[RGDf-N(Me)V-]

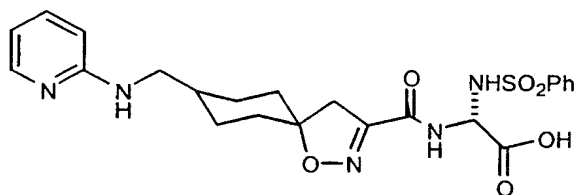
20 108. The method of Claim 56 wherein the integrin antagonist is

-290-



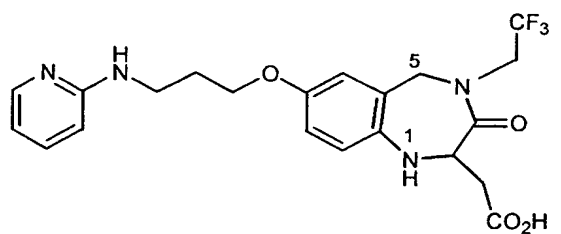
109. The method of Claim 56 wherein the integrin antagonist is

5



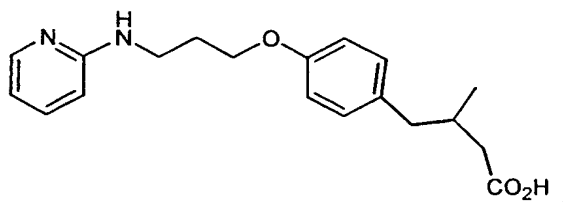
110. The method of Claim 56 wherein the integrin antagonist is

10



111. The method of Claim 56 wherein the integrin antagonist is

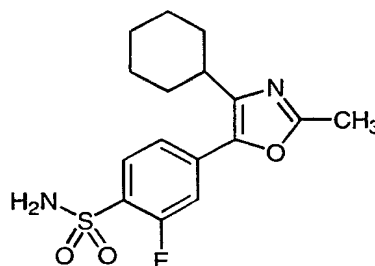
15



112. A combination comprising a cyclooxygenase-2 inhibitor, an integrin antagonist, and an antineoplastic agent, wherein said antineoplastic agent is selected from the group consisting of anastrozole, calcium carbonate, capecitabine, carboplatin, cisplatin, Cell Pathways CP-461, docetaxel, doxorubicin, etoposide, fluorouracil (5-FU), fluoxymestrine, gemcitabine, goserelin, irinotecan, ketoconazole, letrozol, leucovorin, levamisole, megestrol, mitoxantrone, paclitaxel, raloxifene, retinoic acid, tamoxifen, thiotepa, topotecan, toremifene, vinorelbine, vinblastine, vincristine, selenium (selenomethionine), ursodeoxycholic acid, sulindac sulfone, exemestane and eflornithine (DFMO).

113. The combination of Claim 112 wherein the cyclooxygenase-2 inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

1)



JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide,

2)

-292-

5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine,

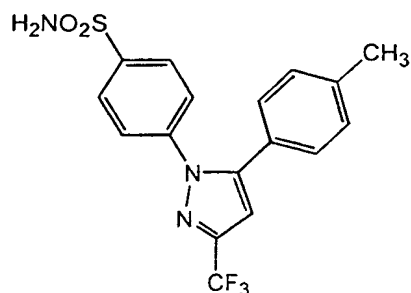
3)

2-(3,5-difluorophenyl)-3-4-

5

(methylsulfonyl)phenyl)-2-cyclopenten-1-one,

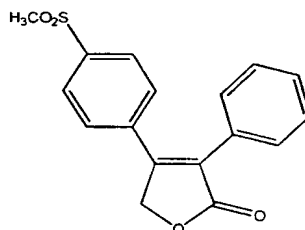
4)



4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide,

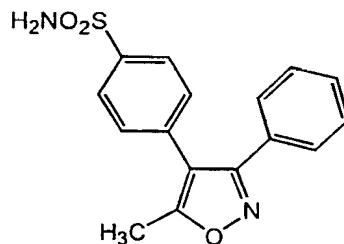
10

5)



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone,

6)

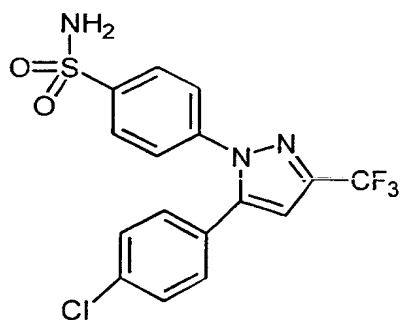


15

4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide,

7) N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide,

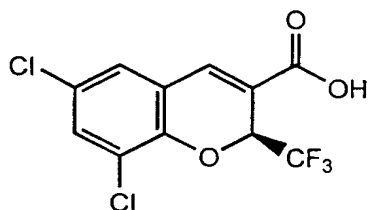
8)



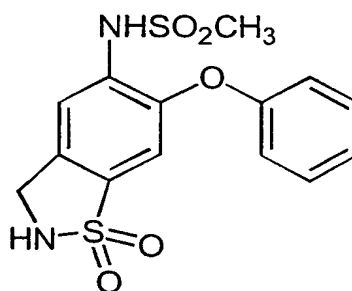
4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,

5

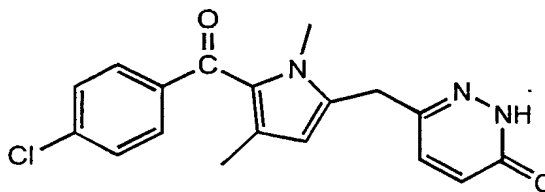
9)



10)



11)

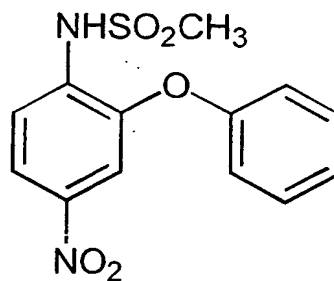


10

6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

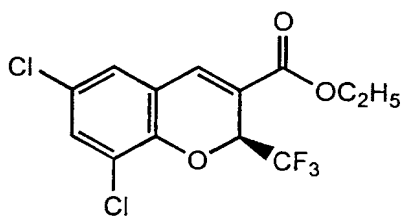
12)

-294-



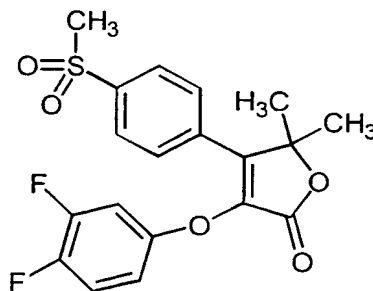
N-(4-nitro-2-phenoxyphenyl)methanesulfonamide,

13)



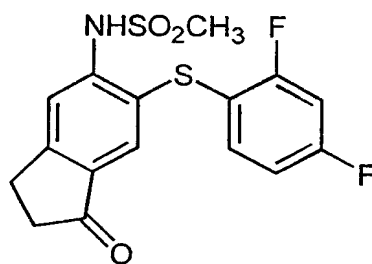
5

14)



3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,

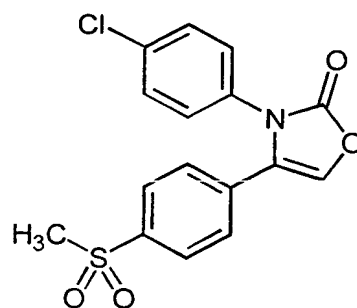
15)



10

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

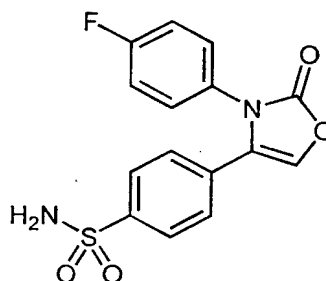
16)



3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

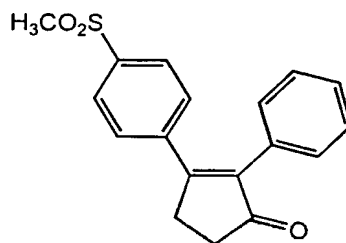
5

17)



4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

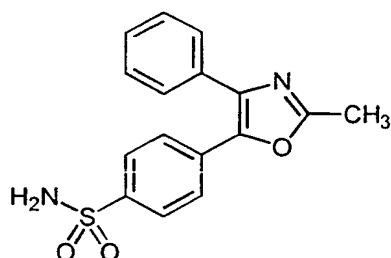
18)



10

3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,

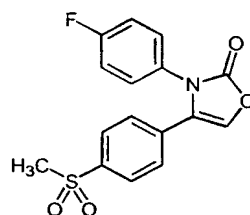
19)



4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,

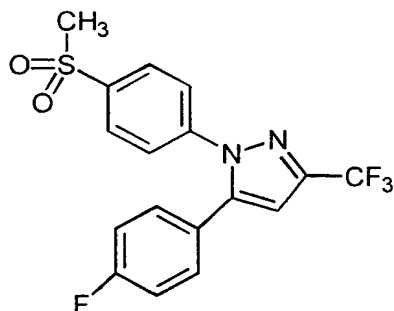
5

20)



3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

21)



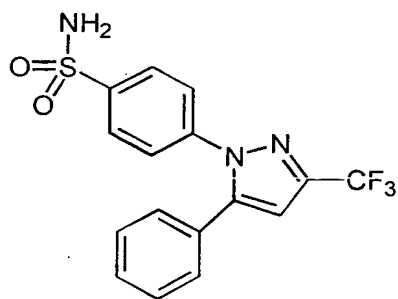
10

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,



-297-

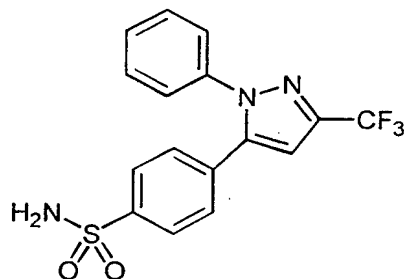
22)



4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

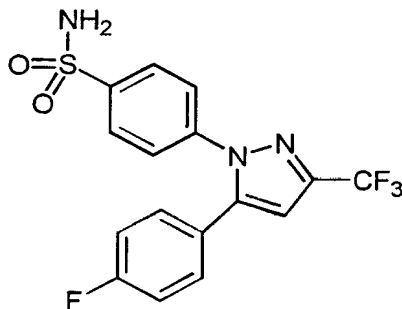
5

23)



4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,

24)

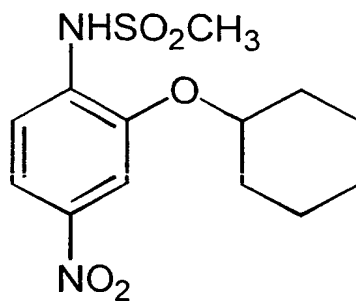


10

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

-298-

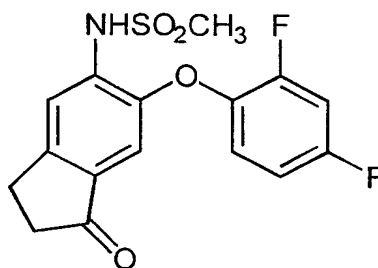
25)



N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide,

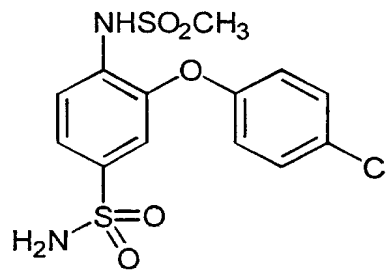
5

26)



N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

27)

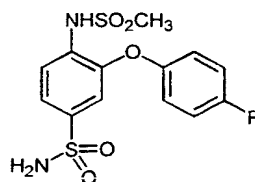


10

3-(4-chlorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide,

-299-

28)

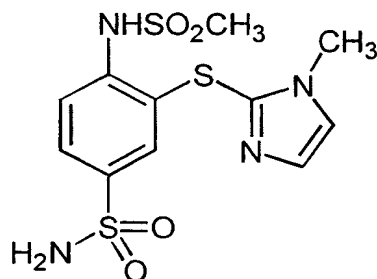


3-(4-fluorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

5

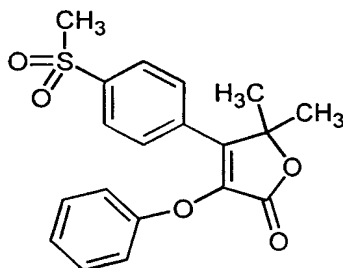
29)



3-[(1-methyl-1H-imidazol-2-yl)thio]-4

[(methylsulfonyl)amino]benzenesulfonamide,

30)

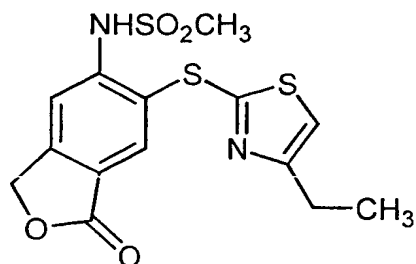


10

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-  
phenoxy-2(5H)-furanone,

-300-

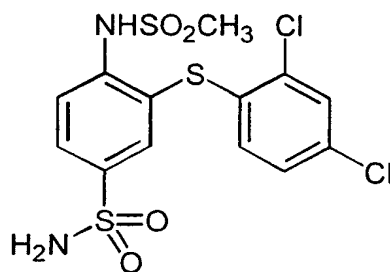
31)



N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

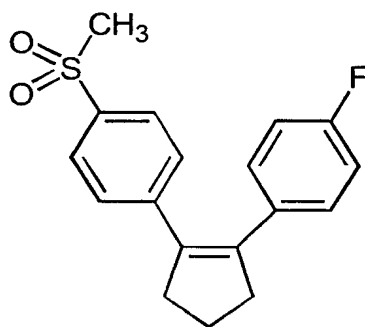
5

32)



3-[(2,4-dichlorophenyl)thio]-4-[(methanesulfonyl)amino]benzenesulfonamide,

33)

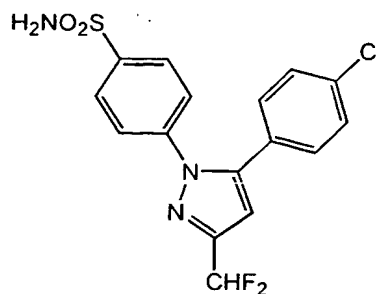


1-fluoro-4-[2-[4-(methanesulfonyl)phenyl]cyclopenten-1-yl]benzene,

10

-301-

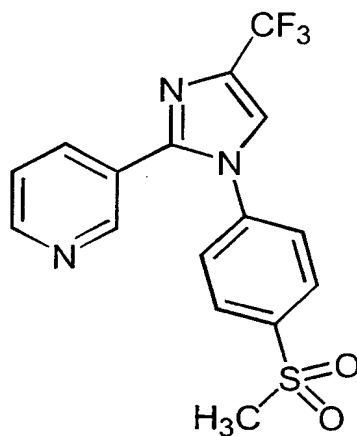
34)



4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

5

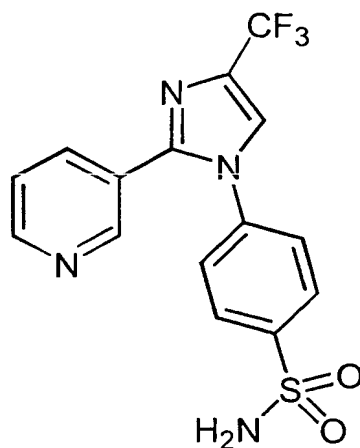
35)



3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

-302-

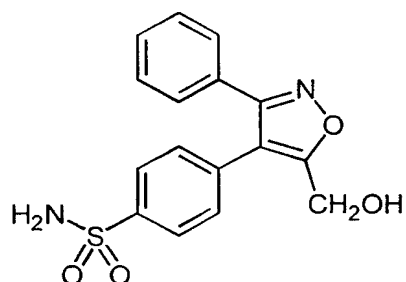
36)



4-[2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide,

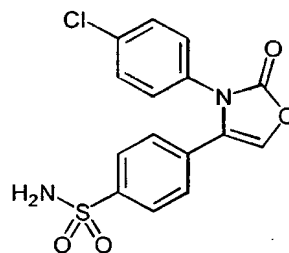
5

37)



4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

38)

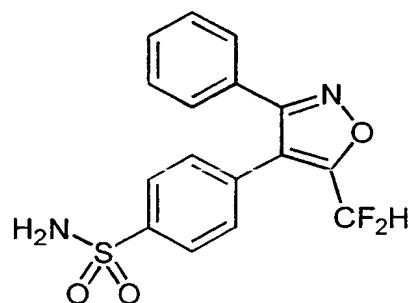


10

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

-303-

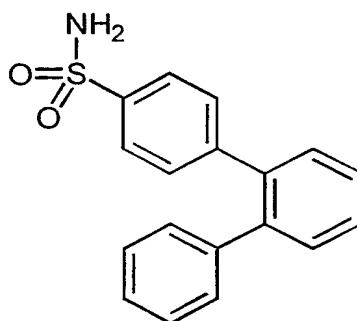
39)



4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

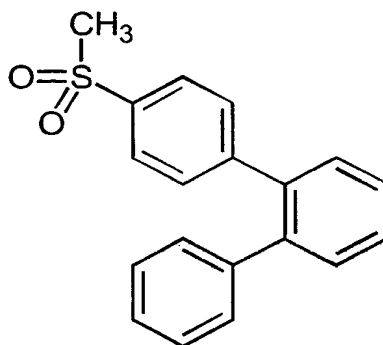
5

40)



[1,1':2',1''-terphenyl]-4-sulfonamide,

41)

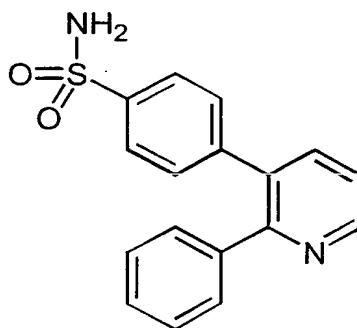


10

4-(methylsulfonyl)-1,1',2],1''-terphenyl,

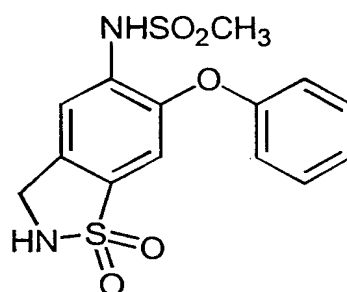
-304-

42)



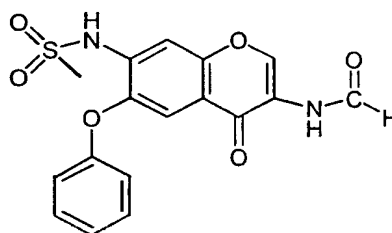
4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

43)



N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and

44)

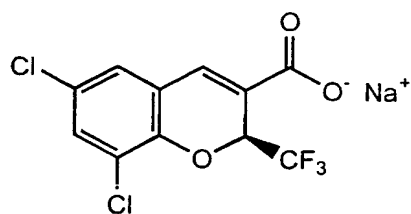


N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

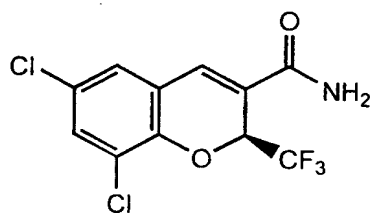


-305-

45)

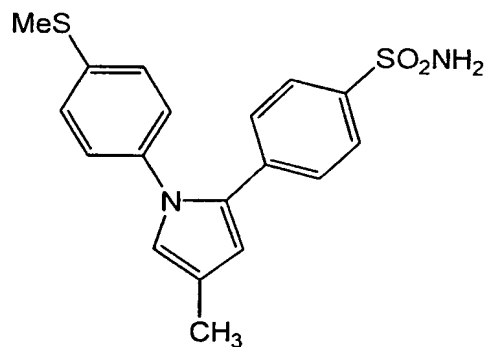


46)



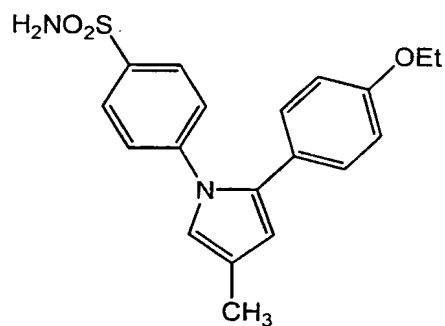
5

47)



, and

48)

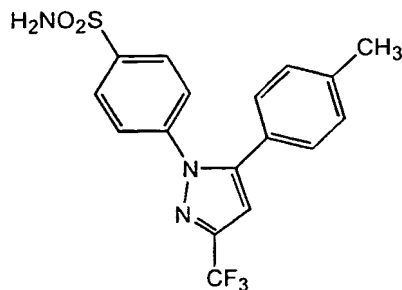


114. The combination of Claim 112 wherein the  
 10 cyclooxygenase-2 inhibitor is 5-chloro-3-(4-(methanesulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.

-306-

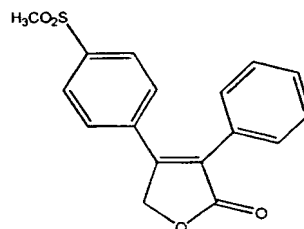
115. The combination of Claim 112 wherein the cyclooxygenase-2 inhibitor is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.

116. The combination of Claim 112 wherein the  
5 cyclooxygenase-2 inhibitor is



4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

117. The combination of Claim 112 wherein the  
10 cyclooxygenase-2 inhibitor is



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone.



gland carcinoma, basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, cavernous, cholangiocarcinoma, chondrosarcoma, choroid plexus papilloma/carcinoma, clear

5 cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma,

10 glucagonoma, hemangiblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intraepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma,

15 leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular

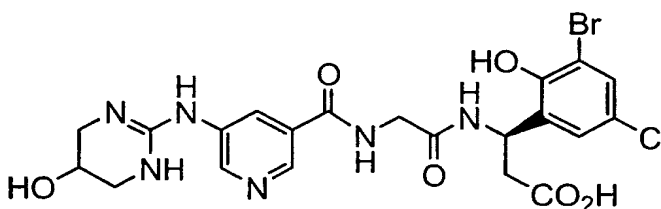
20 melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma,

25 sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous

30 carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor.

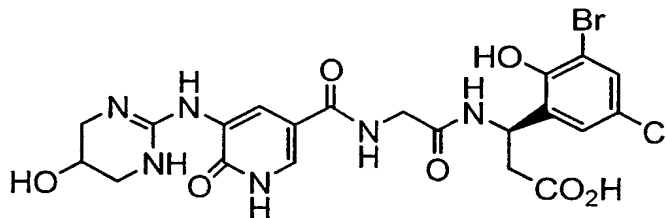
123. The combination of Claim 112 wherein the integrin antagonist is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

1)



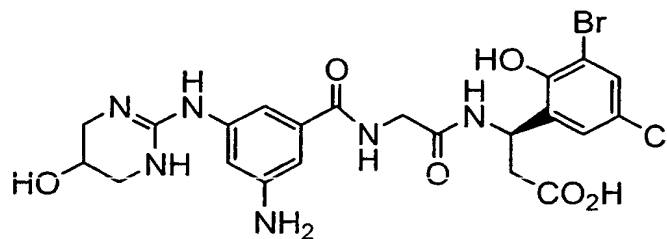
(3R)-N-[[5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

2)



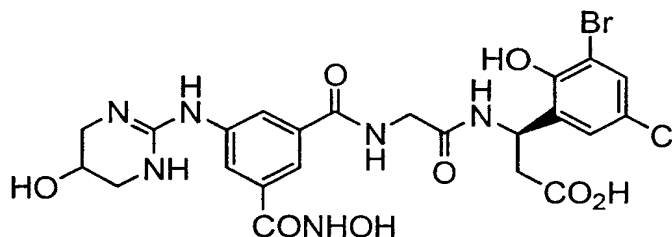
(3R)-N-[[1,6-dihydro-6-oxo-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-L-alanine,

3)



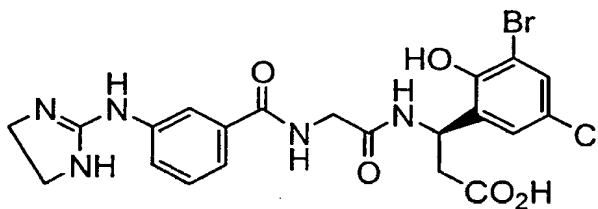
(3R)-N-[3-amino-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

4)



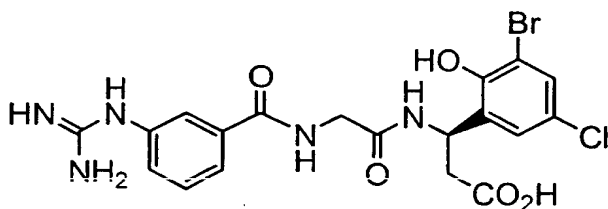
(3R)-N-[3-[(hydroxyamino)carbonyl]-5-[(1,4,5,6-tetrahydro-5-hydroxy)-2-pyrimidinyl]amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

5)



(3R)-N-[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

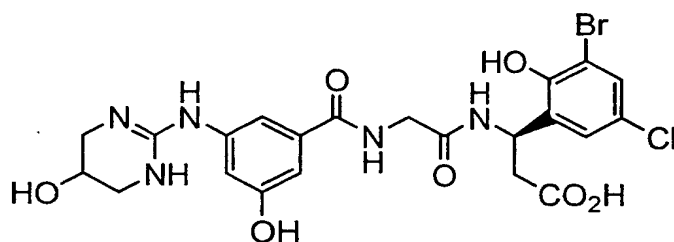
6)



(3R)-N-[3-

[(aminoiminomethyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

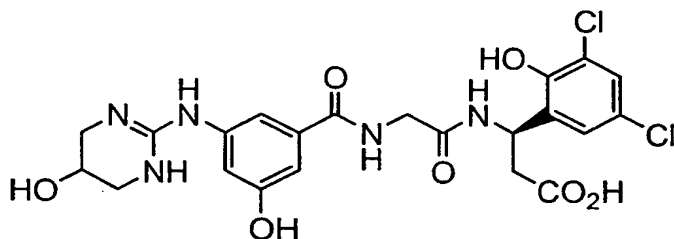
7)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-

hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

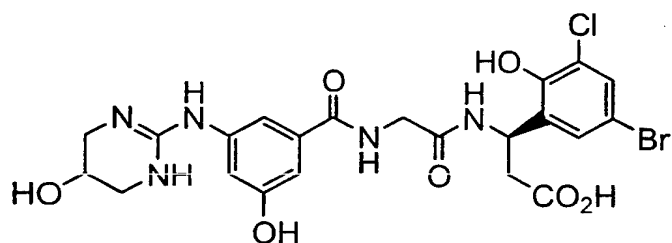
8)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-

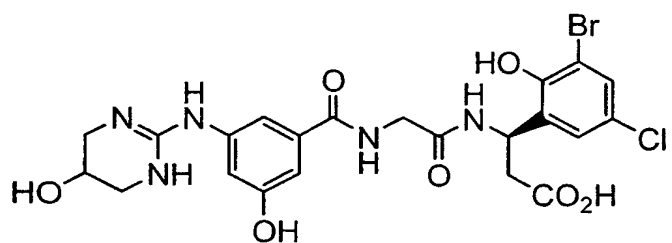
hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3,5-dichloro-2-hydroxyphenyl)-b-alanine,

9)



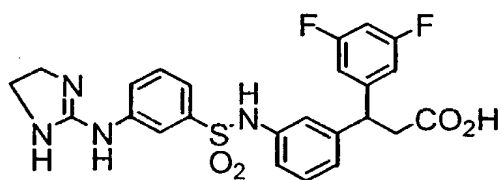
(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(5-bromo-3-chloro-2-hydroxyphenyl)-b-alanine,

10)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

11)

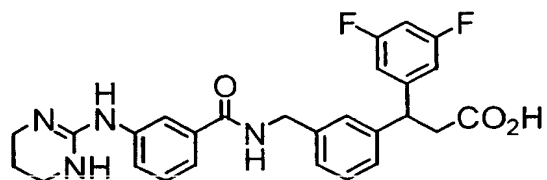


b-[3-[[[3-[[4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]sulfonyl]amino]phenyl]-3,5-difluorobenzenepropanoic acid,



-313-

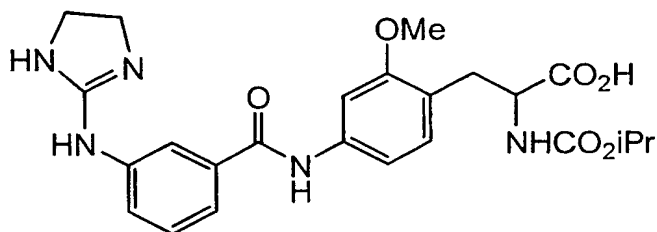
12)



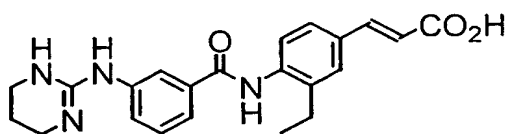
3,5-difluoro-b-[3-[[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]methyl]phenyl]benzenepropanoic acid,

5

13)



14)

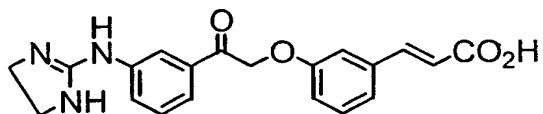


10

(2E)-3-[3-ethyl-4-[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]phenyl]-2-propenoic acid,

15

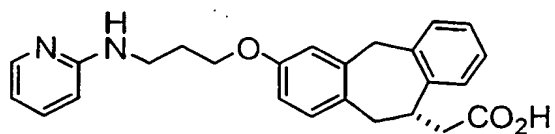
15)



(2E)-3-[3-[2-[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]-2-oxoethoxy]phenyl]-2-propenoic acid,

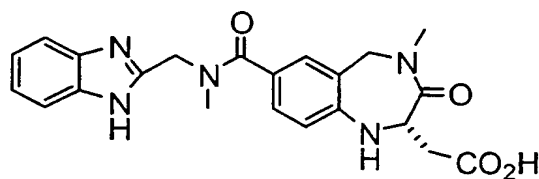
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16)



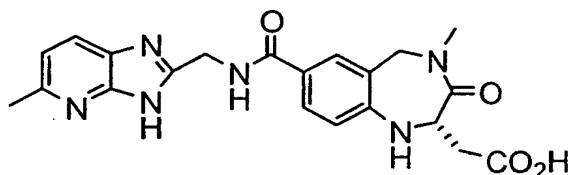
(10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid,

17)



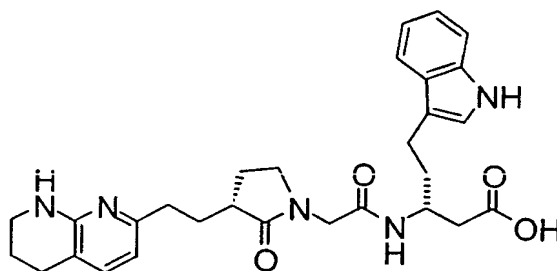
(2S)-7-[[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid,

18)



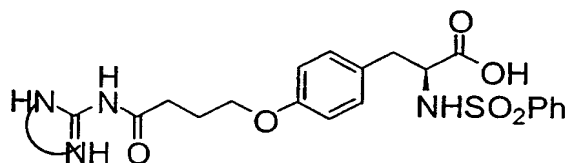
(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid,

19)



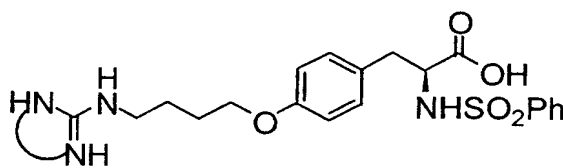
(bR) -b-[[[(3R)-2-oxo-3-[2-(1,5,6,7-tetrahydro-  
1,8-naphthyridin-2-yl)ethyl]-1-  
pyrrolidinyl]acetyl]amino]-1H-indole-3-  
pentanoic acid,

20)

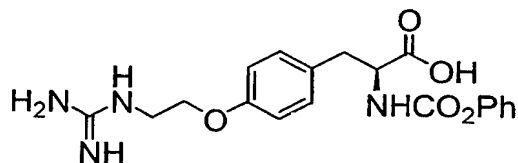


10

21)

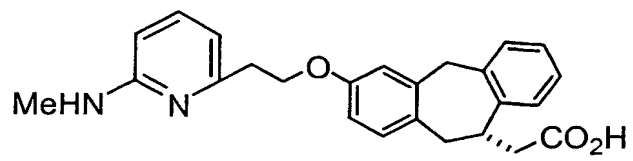


22)



15

23)

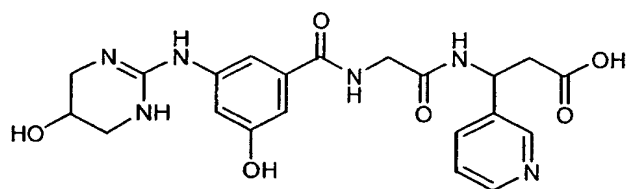


24) Vitaxin antibody(Ixsys),

25) Merck KGaA EMD-121974, cyclo[RGDf-N(Me)V-],

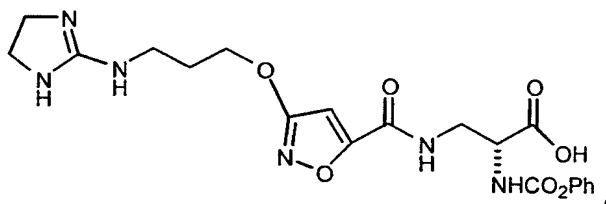
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26)

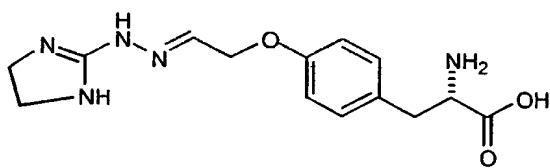


10

27)



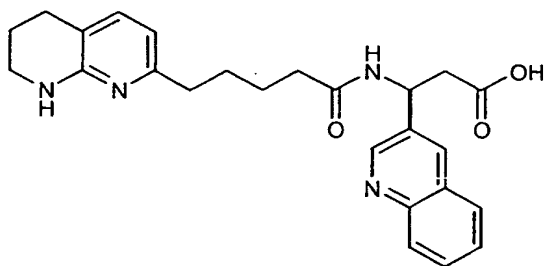
28)



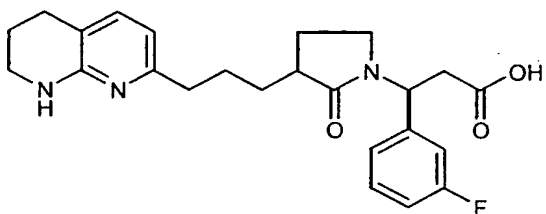
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-317-

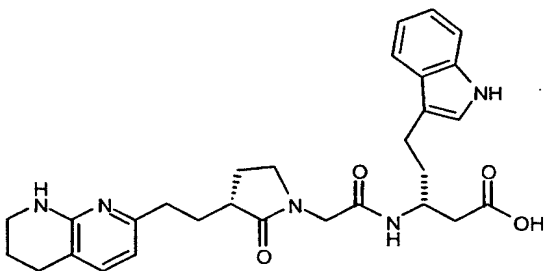
29)



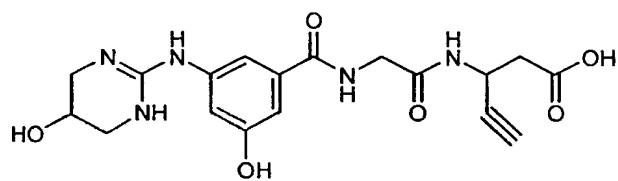
30)



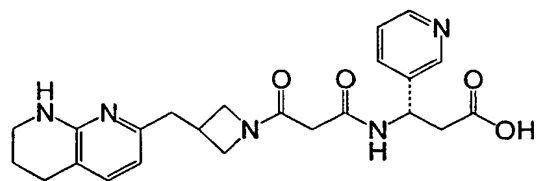
31)



32)

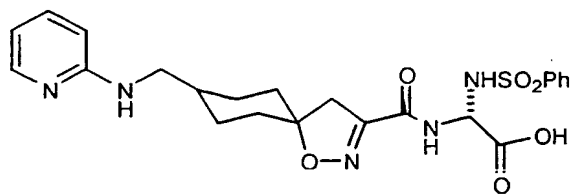


33)



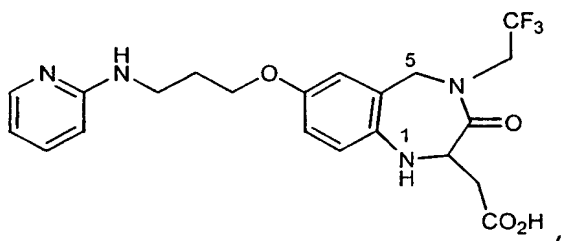
-318-

34)

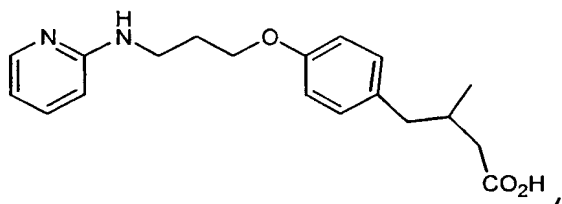


35)

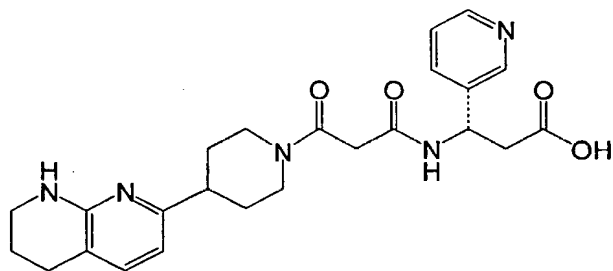
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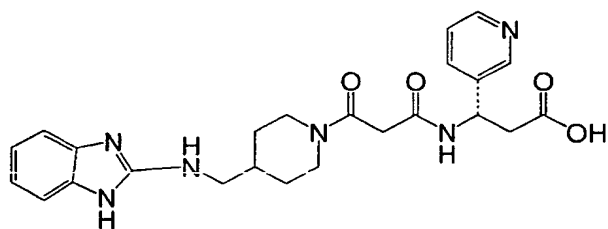
36)



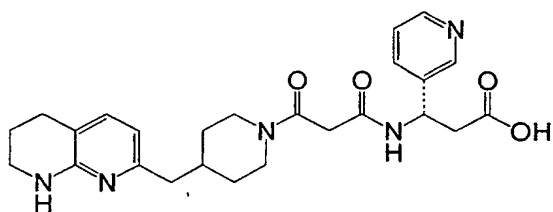
37)



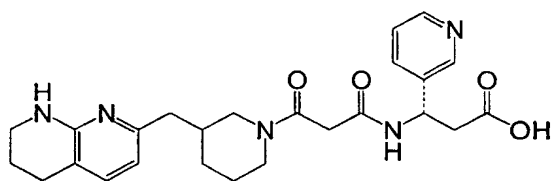
38)



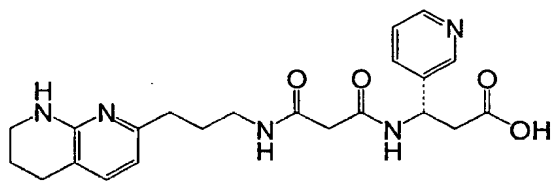
39)



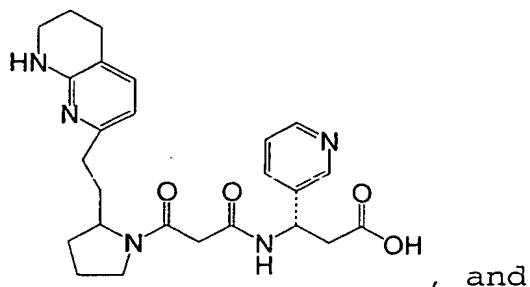
40)



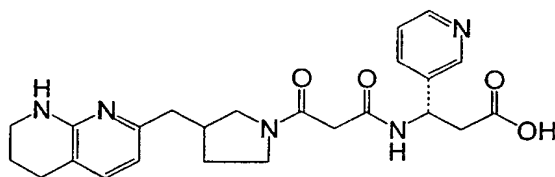
41)



42)

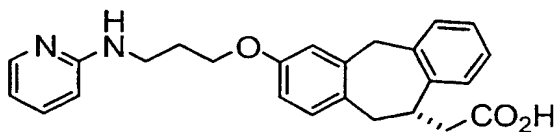


43)



5

124. The combination of Claim 112 wherein the integrin antagonist is



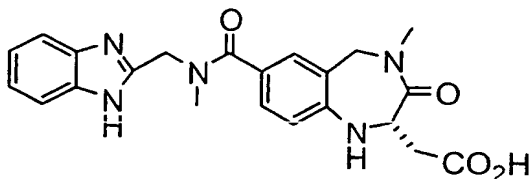
10

(10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid.



-321-

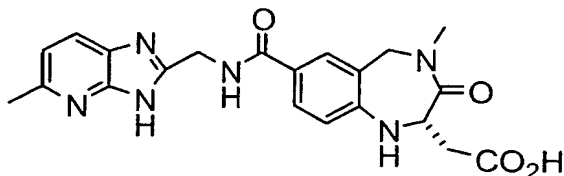
125. The combination of Claim 112 wherein the integrin antagonist is



5

(2S)-7-[[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid.

126. The combination of Claim 112 wherein the integrin antagonist is

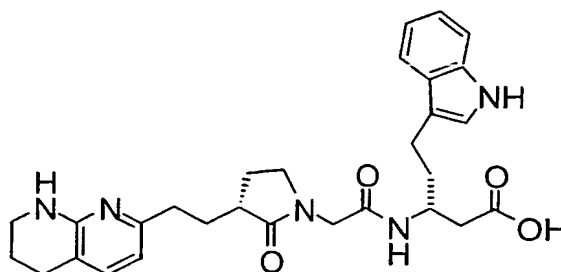


10

(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid.

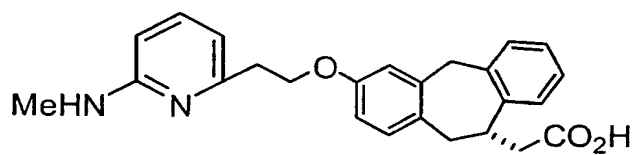
-322-

127. The combination of Claim 112 wherein the integrin antagonist is



5 (bR)-b-[[[(3R)-2-oxo-3-[2-(1,5,6,7-tetrahydro-1,8-naphthyridin-2-yl)ethyl]-1-pyrrolidinyl]acetyl]amino]-1H-indole-3-pentanoic acid.

128. The combination of Claim 112 wherein the  
10 integrin antagonist is



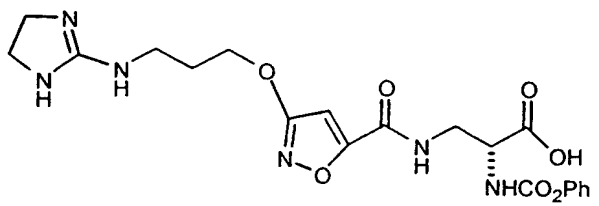
129. The combination of Claim 112 wherein the  
15 integrin antagonist is Vitaxin antibody(Ixsys).

130. The combination of Claim 112 wherein the integrin antagonist is Merck KGaA EMD-121974, cyclo[RGDf-N(Me)V-]

20

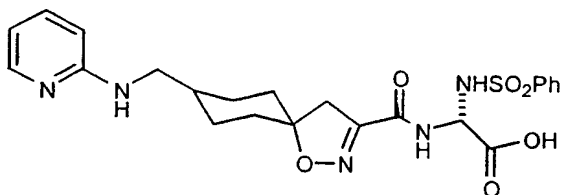
131. The combination of Claim 112 wherein the integrin antagonist is

-323-



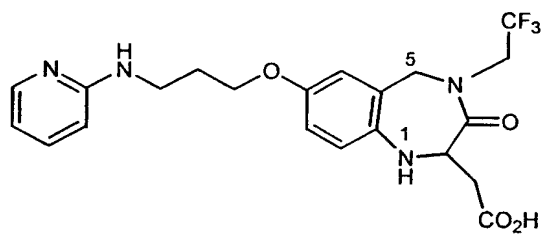
132. The combination of Claim 112 wherein the integrin antagonist is

5



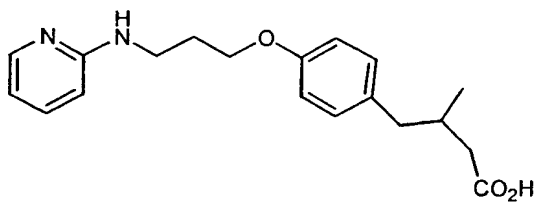
133. The combination of Claim 112 wherein the integrin antagonist is

10



134. The combination of Claim 112 wherein the integrin antagonist is

15



-324-

135. The method of Claim 1 wherein the antineoplastic agent is anastrozole.

136. The method of Claim 1 wherein the  
5 antineoplastic agent is calcium carbonate.

137. The method of claim 1 wherein the antineoplastic agent is exemestane.

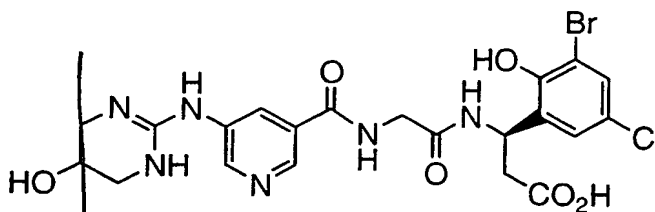
10 138. The method of Claim 56 wherein the antineoplastic agent is anastrozole.

139. The method of Claim 56 wherein the antineoplastic agent is calcium carbonate.

15 140. The method of claim 56 wherein the antineoplastic agent is exemestane.

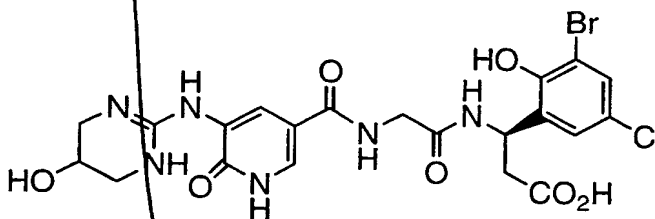
20 141. A method for treating or preventing a neoplasia disorder in a mammal in need of such treatment or prevention, which method comprises administering to said mammal a therapeutically-effective amount of a combination of a cyclooxygenase-2 inhibitor and an integrin antagonist, wherein said integrin antagonist is  
25 selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

1)



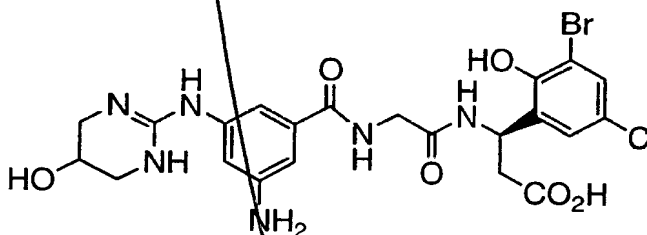
(3R)-N-[[5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

2)



(3R)-N-[[1,6-dihydro-6-oxo-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

3)

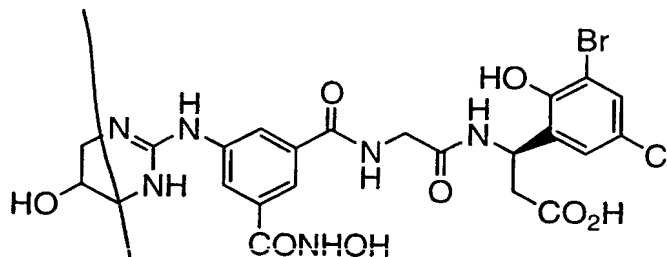


(3R)-N-[3-amino-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

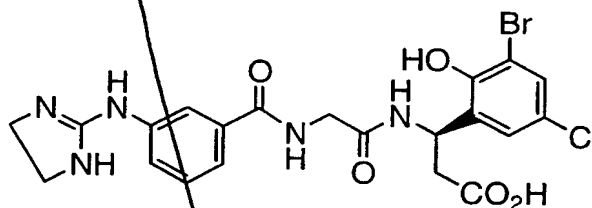
4)

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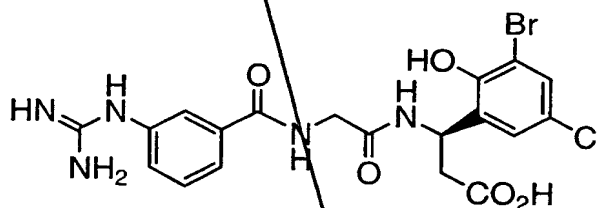
-326-



(3R)-N-[3-[(hydroxyamino)carbonyl]-5-  
[(1,4,5,6-tetrahydro-5-hydroxy)-2-  
pyrimidinyl]amino]benzoyl]glycyl-3-(3-bromo-5-  
chloro-2-hydroxyphenyl)-b-alanine,

5)  
5

(3R)-N-[3-[(4,5-dihydro-1H-imidazol-2-  
yl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-  
hydroxyphenyl)-b-alanine,

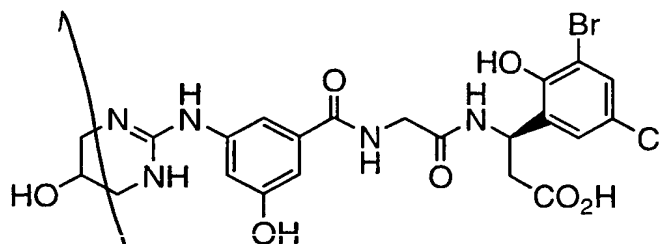
6)  
10

(3R)-N-[3-  
[(aminoiminomethyl)amino]benzoyl]glycyl-3-(3-  
bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

7)  
15

but a  
Cont

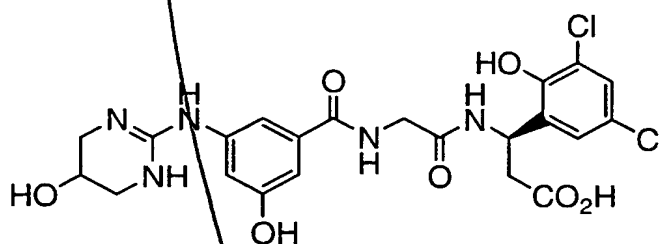
-327-



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

5

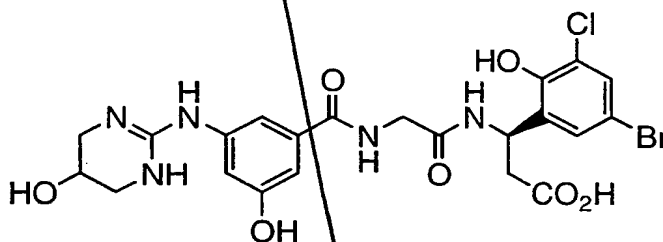
8)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3,5-dichloro-2-hydroxyphenyl)-b-alanine,

10

9)



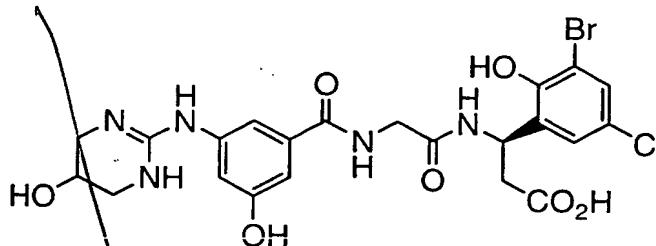
(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(5-bromo-3-chloro-2-hydroxyphenyl)-b-alanine,

15

10)

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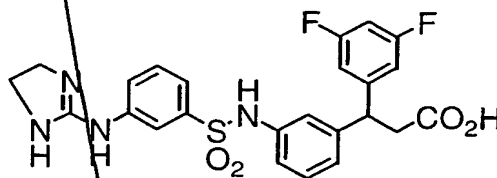
-328-



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

5

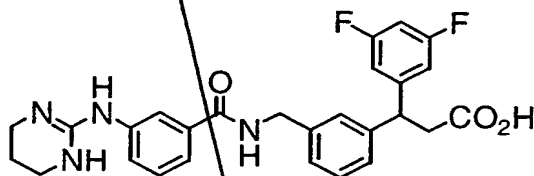
11)



b-[3-[[[3-[[4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]sulfonyl]amino]phenyl]-3,5-difluorobenzenepropanoic acid,

10

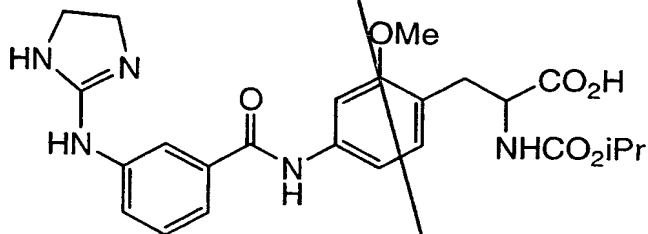
12)



3,5-difluoro-b-[3-[[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]methyl]phenyl]benzenepropanoic acid,

15

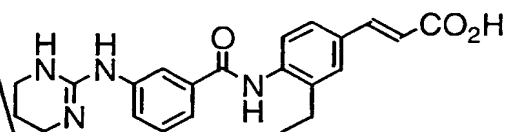
13)



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a  
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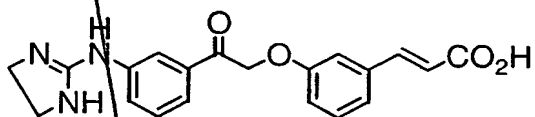
14)



(2E)-3-[3-ethyl-4-[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]phenyl]-2-propenoic acid,

5

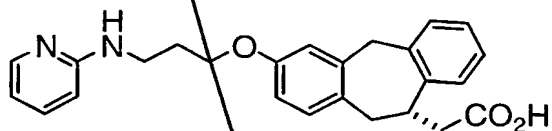
15)



(2E)-3-[3-[2-[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]-2-oxoethoxy]phenyl]-2-propenoic acid,

10

16)

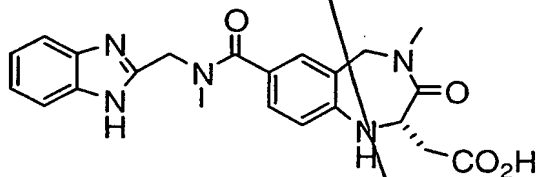


(10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid,

15

20

17)

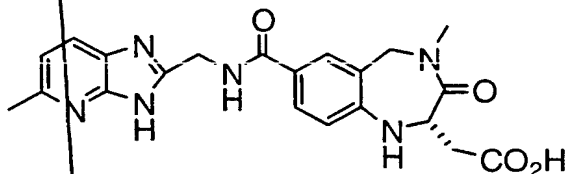


(2S)-7-[[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetramethyl-2,3,4,5-tetrahydro-1H-benzimidazol-2-yl]-2-propenoic acid,

-330-

tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid,

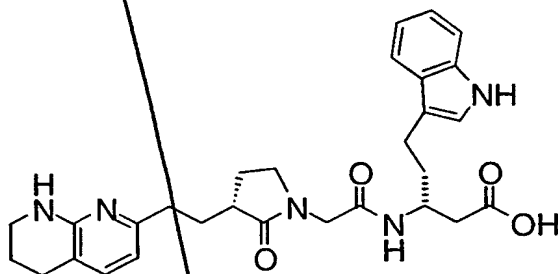
18)



5

(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid,

19)

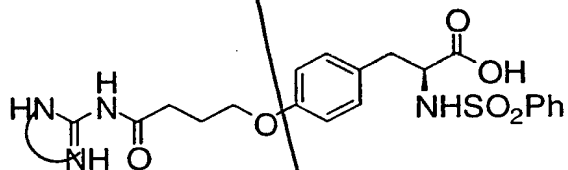


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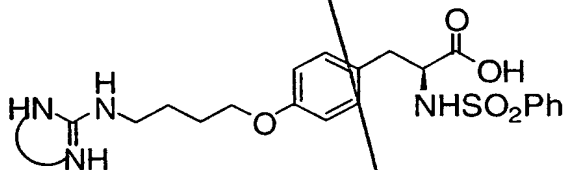
(bR)-b-[[[(3R)-2-oxo-3-[2-(1,5,6,7-tetrahydro-1,8-naphthyridin-2-yl)ethyl]-1-pyrrolidinyl]acetyl]amino]-1H-indole-3-pentanoic acid,

15

20)



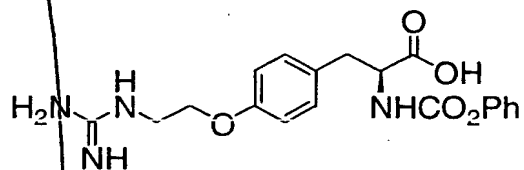
21)



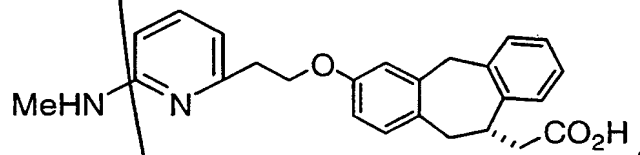
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-331-

22)



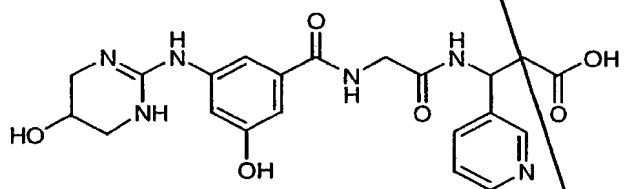
23)



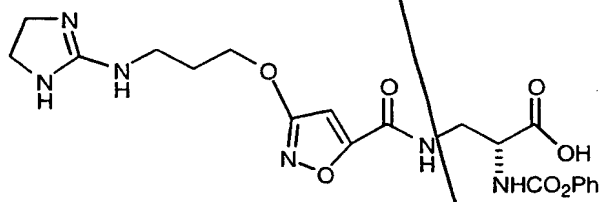
24) Vitaxin antibody(Ixsys),

25) Merck KGaA EMD-121974, cyclo[RGDf-N(Me)V-],

26)



27)

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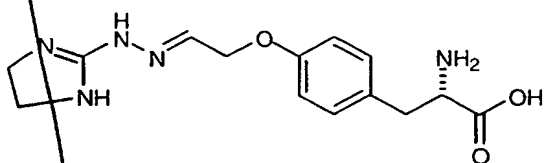
5

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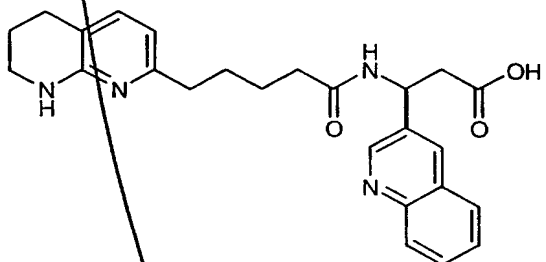
15

-332-

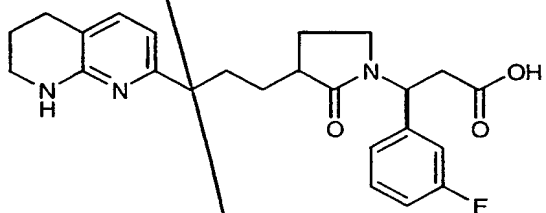
28)



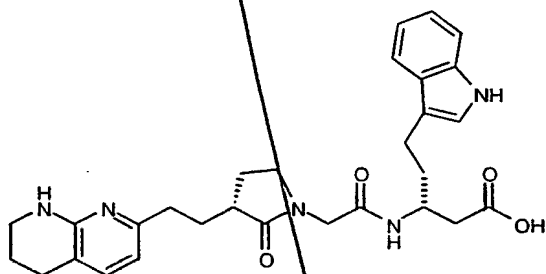
29)



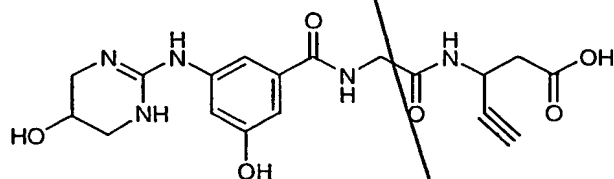
30)



31)



32)

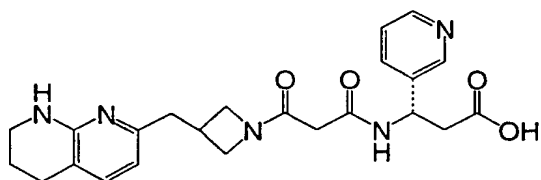
Sub a!  
Cont

5

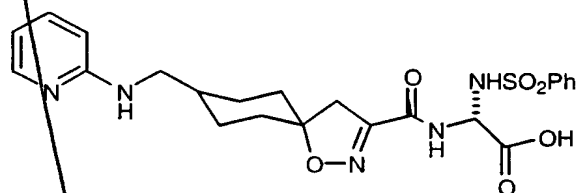
10

-333-

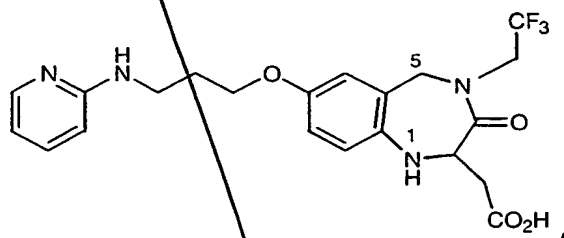
33)



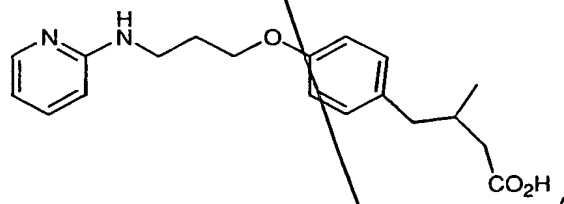
34)



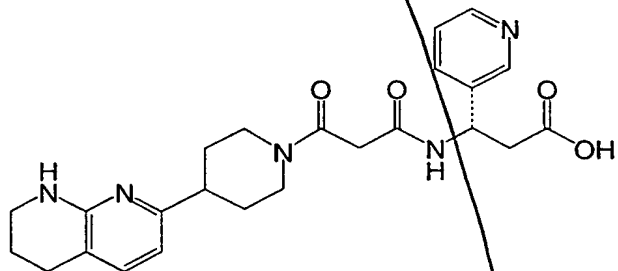
35)



36)



37)



38)

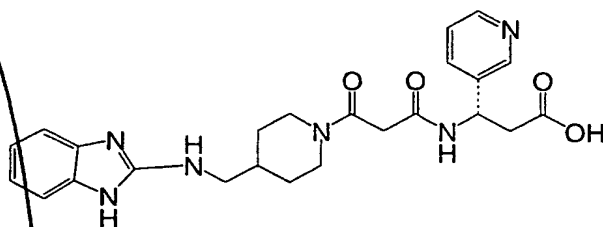
Sub a'  
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5

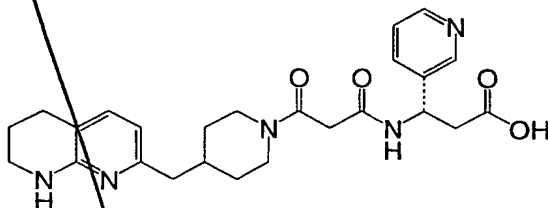
10

-334-

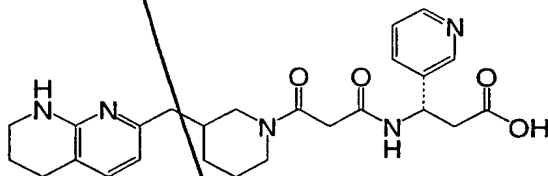
39)



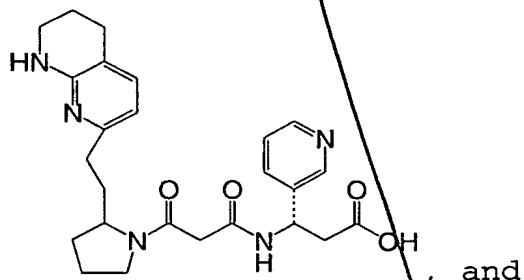
40)



41)



42)



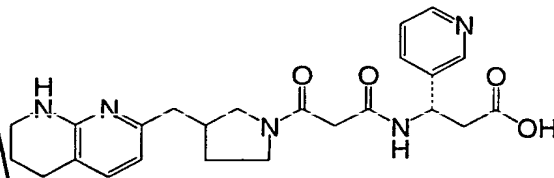
, and

Sub a!  
Cont

5

10

43)



5 142. The method of Claim 141 comprising  
administering to said mammal a therapeutically-effective  
amount of a combination of an cyclooxygenase-2  
inhibitor, an integrin antagonist, and an antineoplastic  
agent, wherein the antineoplastic agent is selected from  
10 the group consisting of anastrozole, calcium carbonate,  
capecitabine, carboplatin, cisplatin, Cell Pathways CP-  
461, docetaxel, doxorubicin, etoposide, fluorouracil (5-  
FU), fluoxymestrine, gemcitabine, goserelin, irinotecan,  
ketoconazole, letrozol, leucovorin, levamisole,  
15 megestrol, mitoxantrone, paclitaxel, raloxifene,  
retinoic acid, tamoxifen, thiotepa, topotecan,  
toremifene, vinorelbine, vinblastine, vincristine,  
selenium (selenomethionine), ursodeoxycholic acid,  
sulindac sulfone and eflornithine (DFMO).

20

143. The method of Claim 141 comprising  
administering to said mammal a therapeutically-effective  
amount of a combination of radiation, a cyclooxygenase-2  
inhibitor and an integrin antagonist.

25

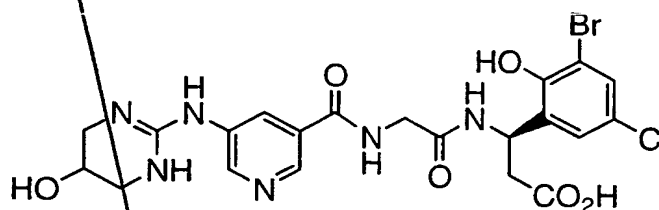
144. A combination comprising a cyclooxygenase-2  
inhibitor and an integrin antagonist, wherein said  
integrin antagonist is selected from compounds, and

Sub A!  
Cont

-336-

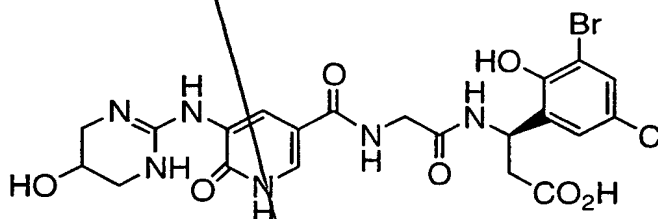
their pharmaceutically acceptable salts thereof, of the group consisting of:

1)



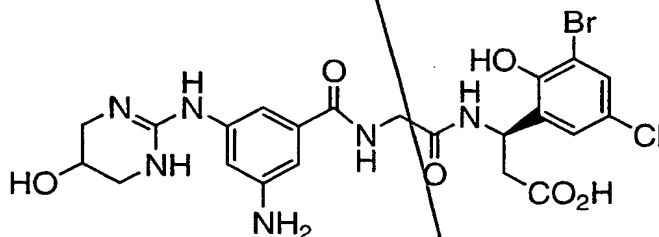
(3R)-N-[[5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

2)



(3R)-N-[[1,6-dihydro-6-oxo-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]-3-pyridinyl]carbonyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

3)



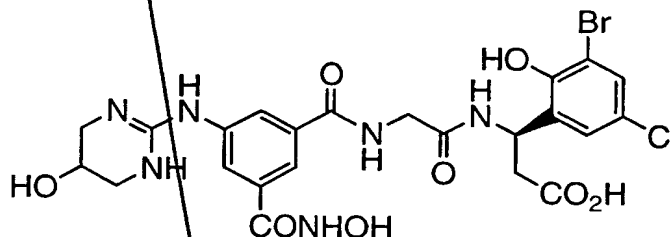


-337-

(3R)-N-[3-amino-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

5

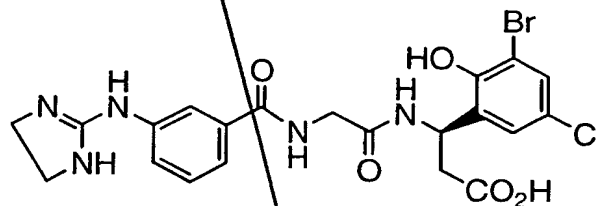
4)



(3R)-N-[3-[(hydroxyamino)carbonyl]-5-[(1,4,5,6-tetrahydro-5-hydroxy)-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

10

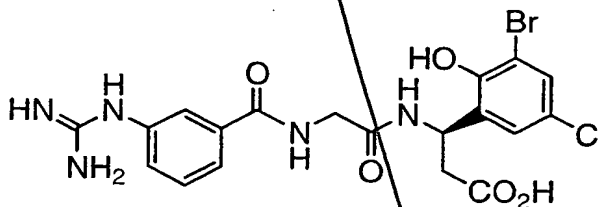
5)



(3R)-N-[3-[(4-,5-dihydro-1H-imidazol-2-yl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

15

6)



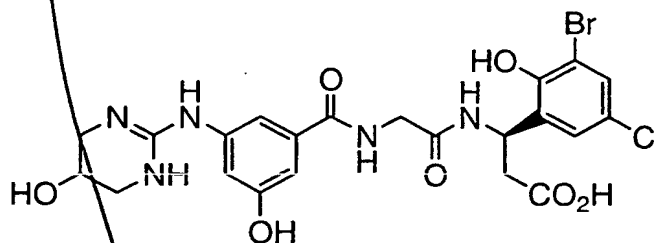
(3R)-N-[3-[(aminoiminomethyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

20

Sub B  
Cont

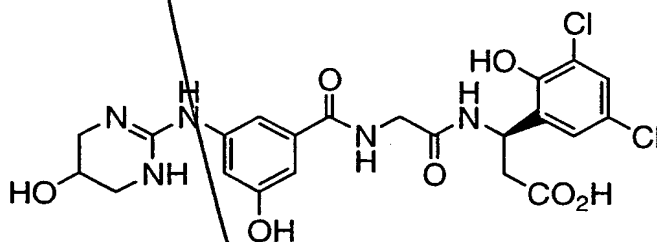
-338-

7)



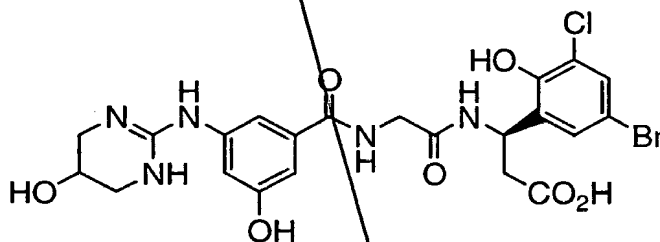
(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

8)



(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3,5-dichloro-2-hydroxyphenyl)-b-alanine,

9)

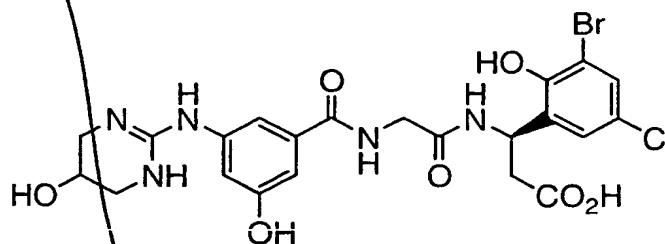


(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(5-bromo-3-chloro-2-hydroxyphenyl)-b-alanine,

10)

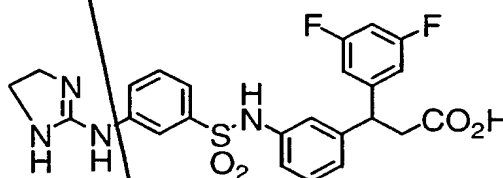
Sub a  
Cont

-339-



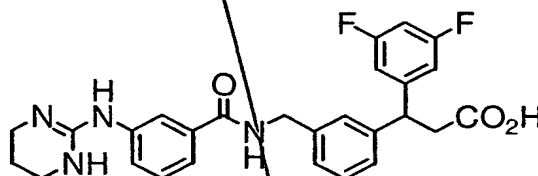
(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine,

5 11)



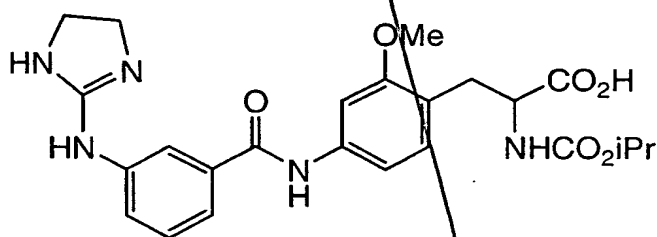
b-[3-[[[3-[[4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]sulfonyl]amino]phenyl]-3,5-difluorobenzenepropanoic acid,

10 12)



3,5-difluoro-b-[3-[[[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]benzoyl]amino]methyl]phenyl]benzenepropanoic acid,

15 13)

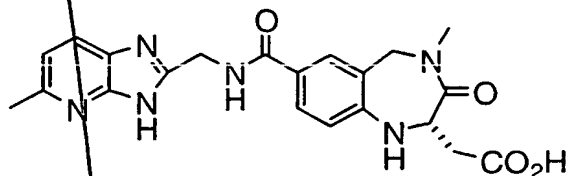




-341-

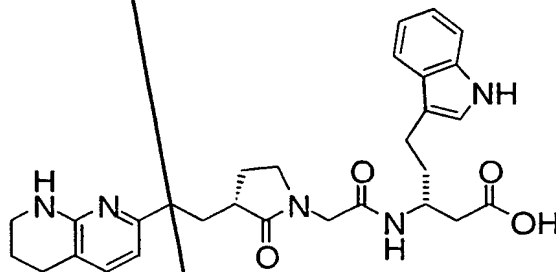
tetrahydro-4-methyl-3-oxo-1H-1,4-  
benzodiazepine-2-acetic acid,

18)



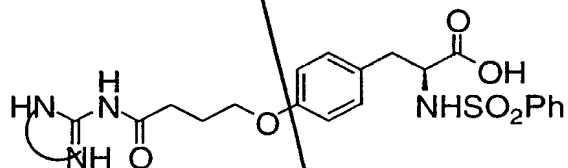
(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-  
methyl-1H-imidazo[4,5-b]pyridin-2-  
yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-  
benzodiazepine-2-acetic acid,

19)

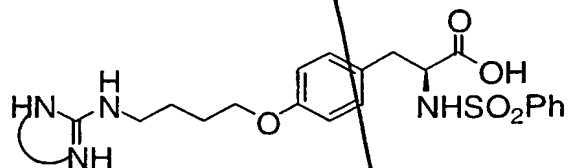


(bR)-b-[[[(3R)-2-oxo-3-[2-(1,5,6,7-tetrahydro-  
1,8-naphthyridin-2-yl)ethyl]-1-  
pyrrolidinyl]acetyl]amino]-1H-indole-3-  
pentanoic acid,

20)

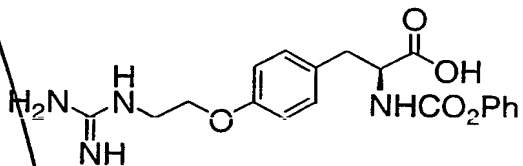


21)

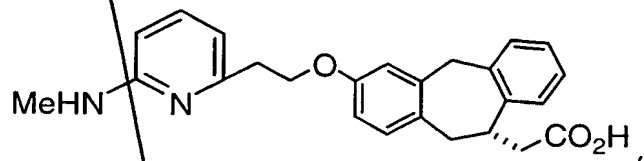


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22)



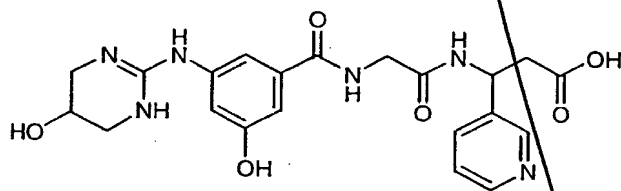
23)



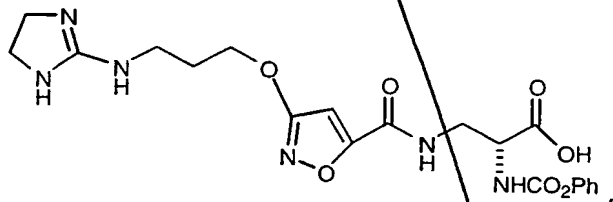
24) Vitaxin antibody (Ixsys),

25) Merck KGaA EMD-121974, cyclo[RGdf-N(Me)V-],

26)

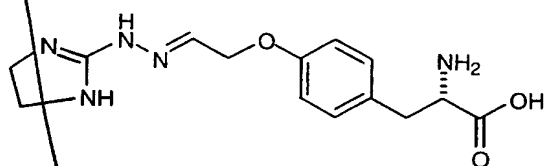


27)

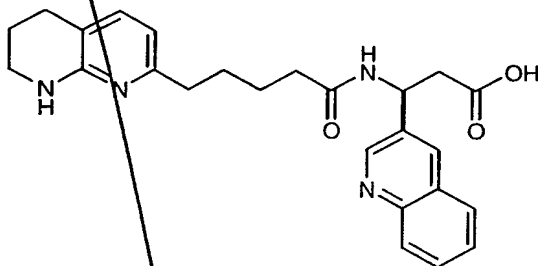


-343-

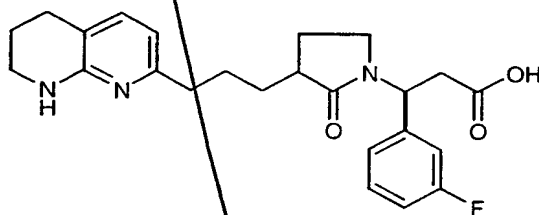
28)



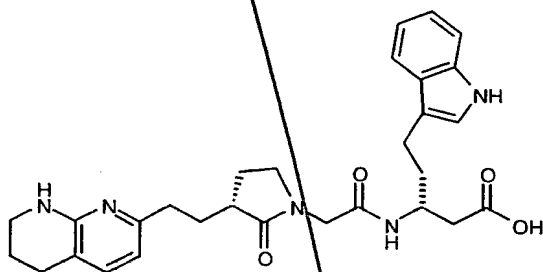
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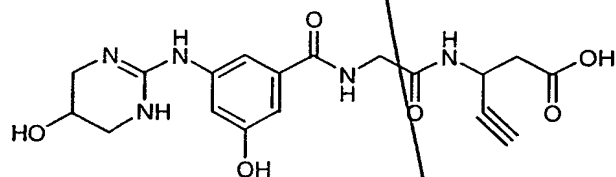
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31)



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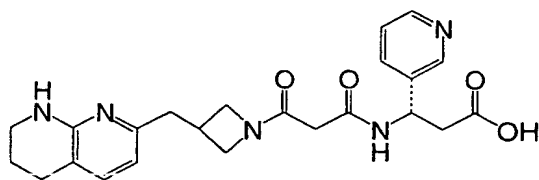
Sub 1  
Cont

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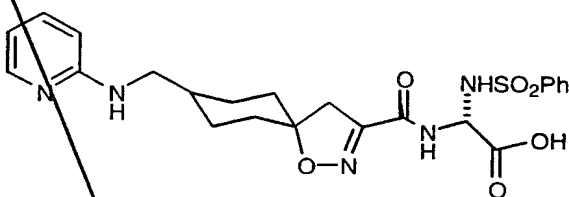
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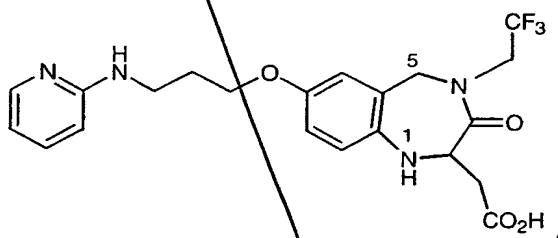
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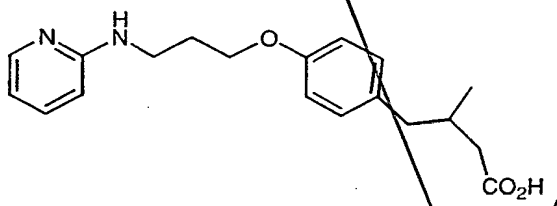
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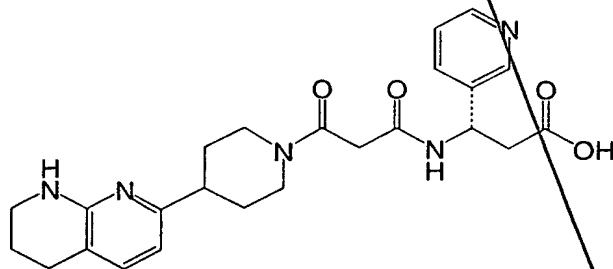
35)



36)



37)



38)

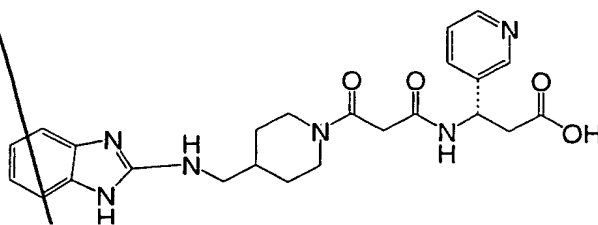
Sub 1  
Cont

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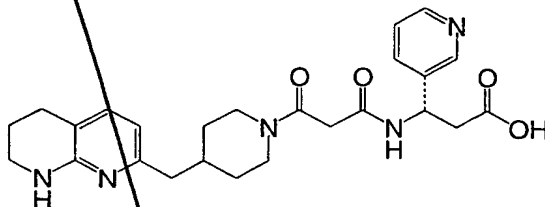


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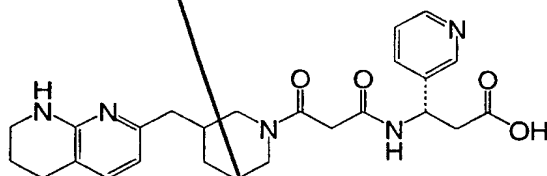
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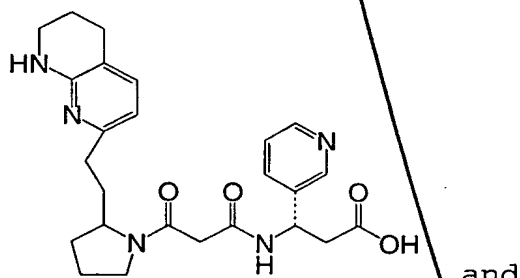
40)



41)



42)



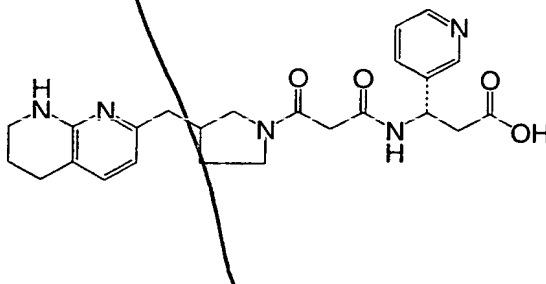
and

Sub a  
Cont

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43)



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Sub 1  
Contd